

Obesity is a Disease

2022 EASO Obesity Masterclass Summer School
Les Pensieres of the Fondation Merieux
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Obesity is a disease

Luca Busetto – Disclosures

- Novo Nordisk
- Bruno Farmaceutici
- Rythm
- Pronokal
- Therascience
- Enzymmanagement

Obesity is a disease

World Obesity Federation Position Statement

Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation

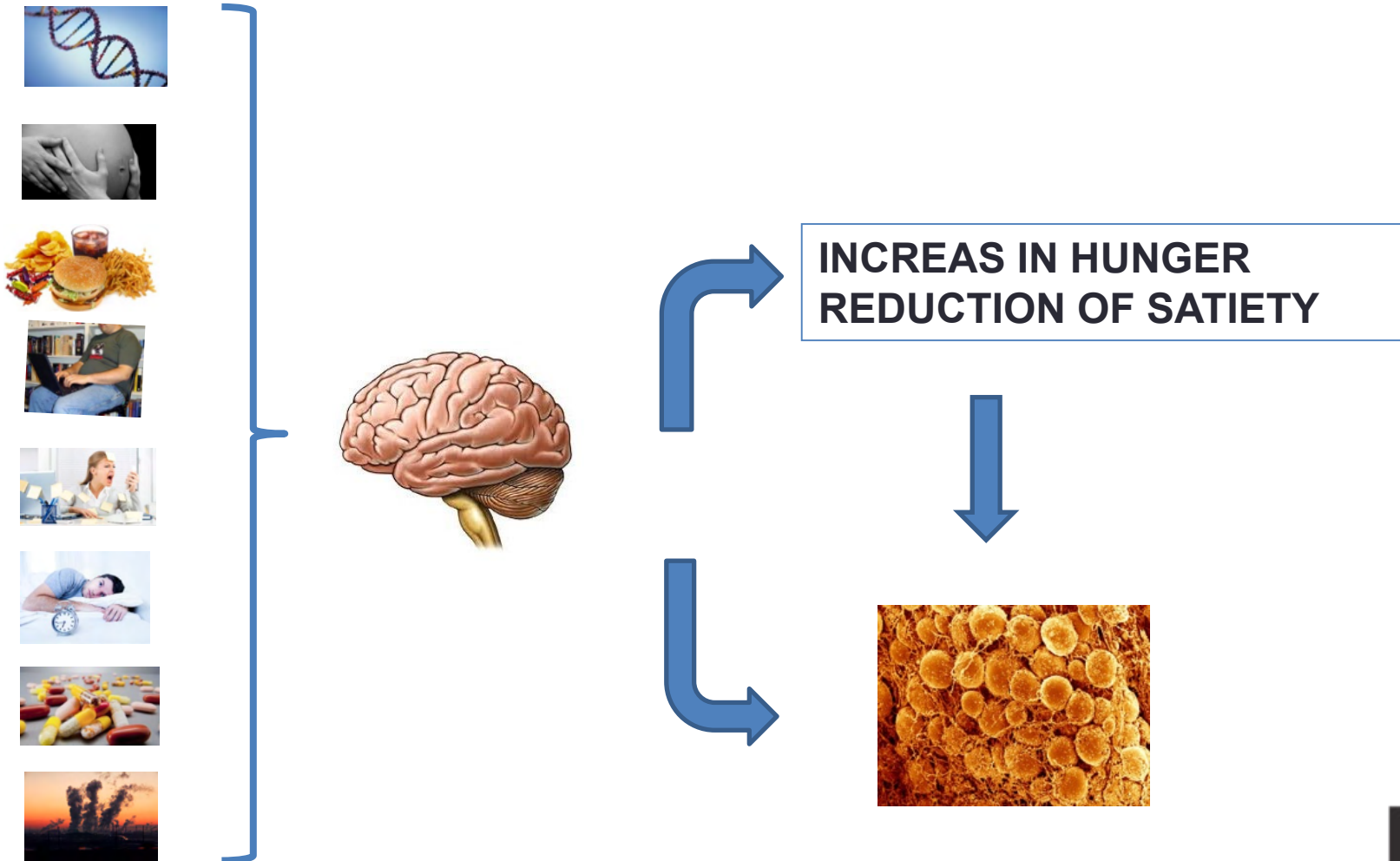
Bray GA et al. *Obes Rev* 2017;18:715

Obesity is a chronic disease

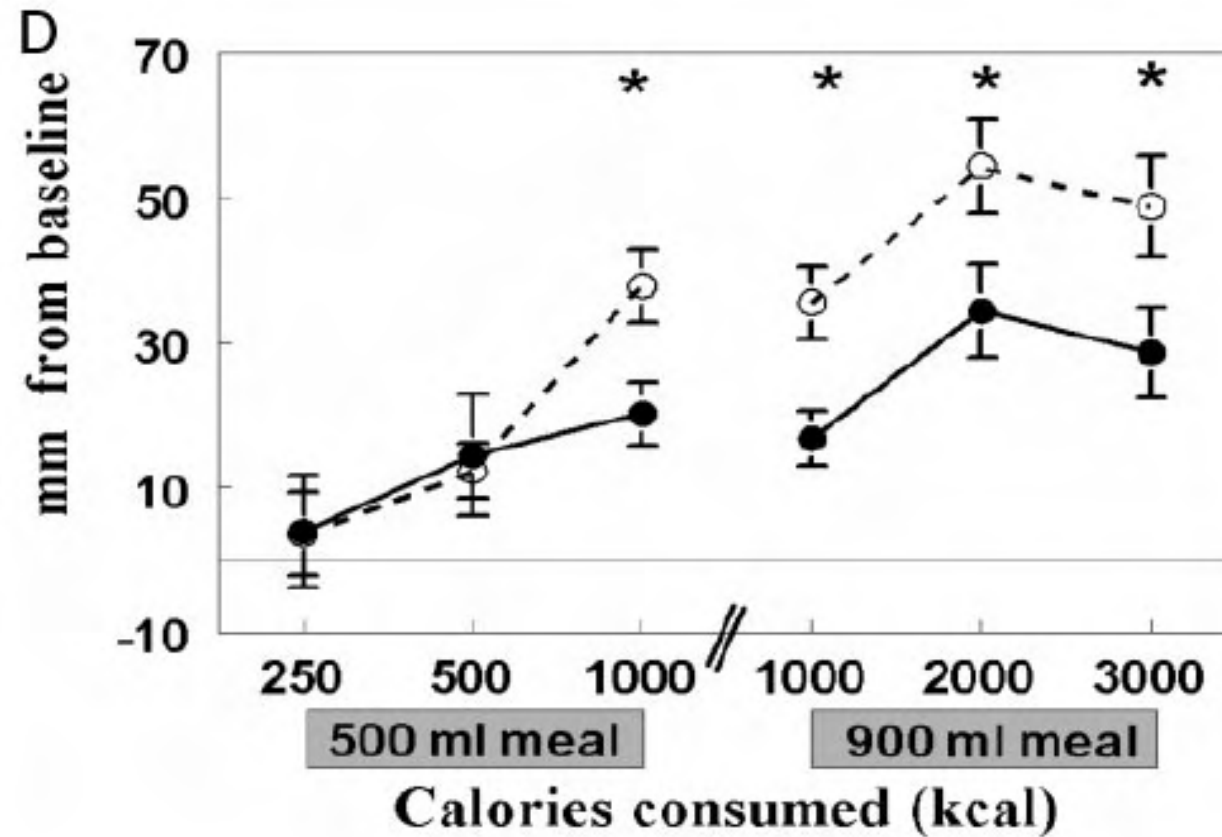
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Obesity is a chronic disease

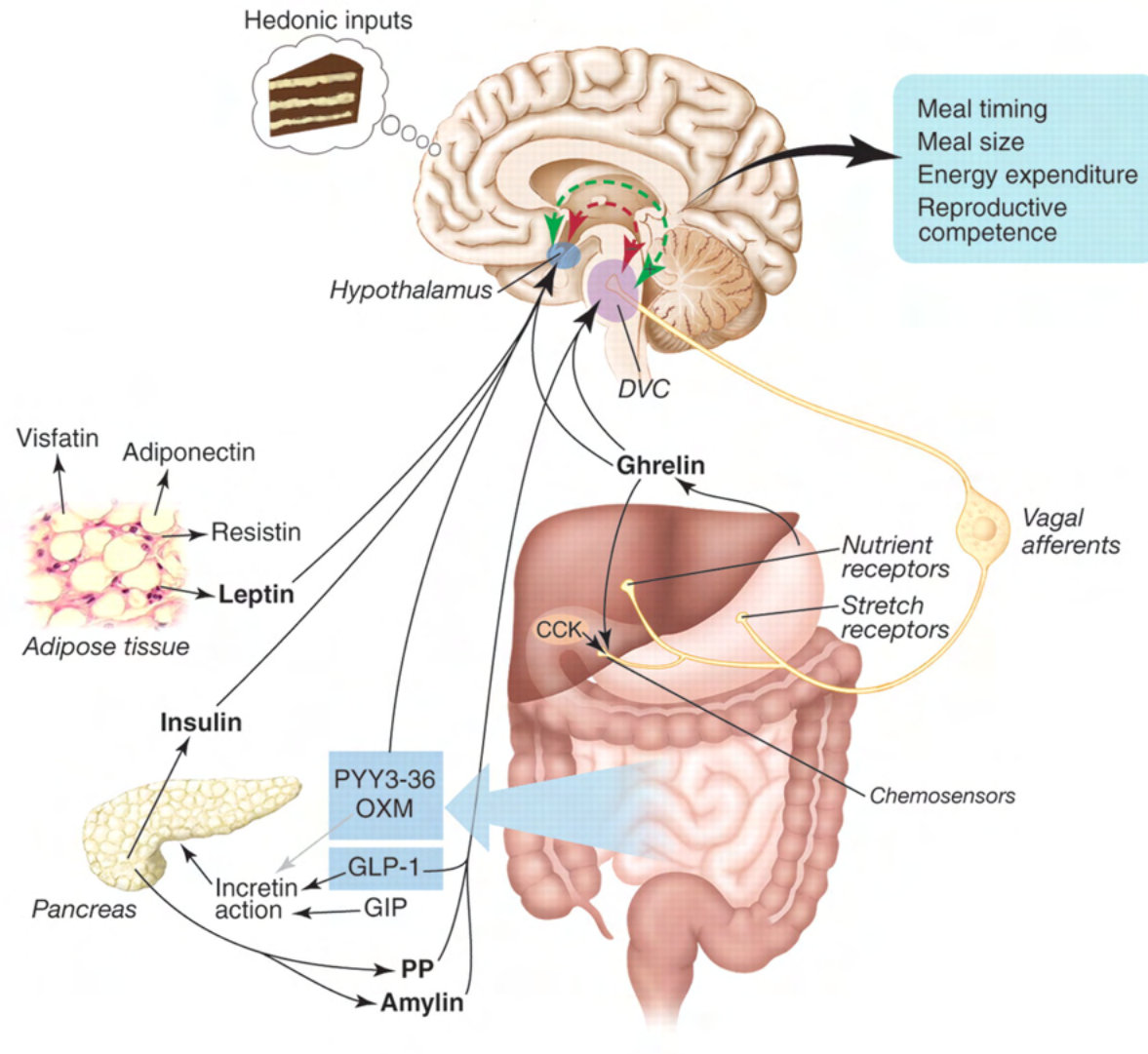


Obesity is a chronic disease



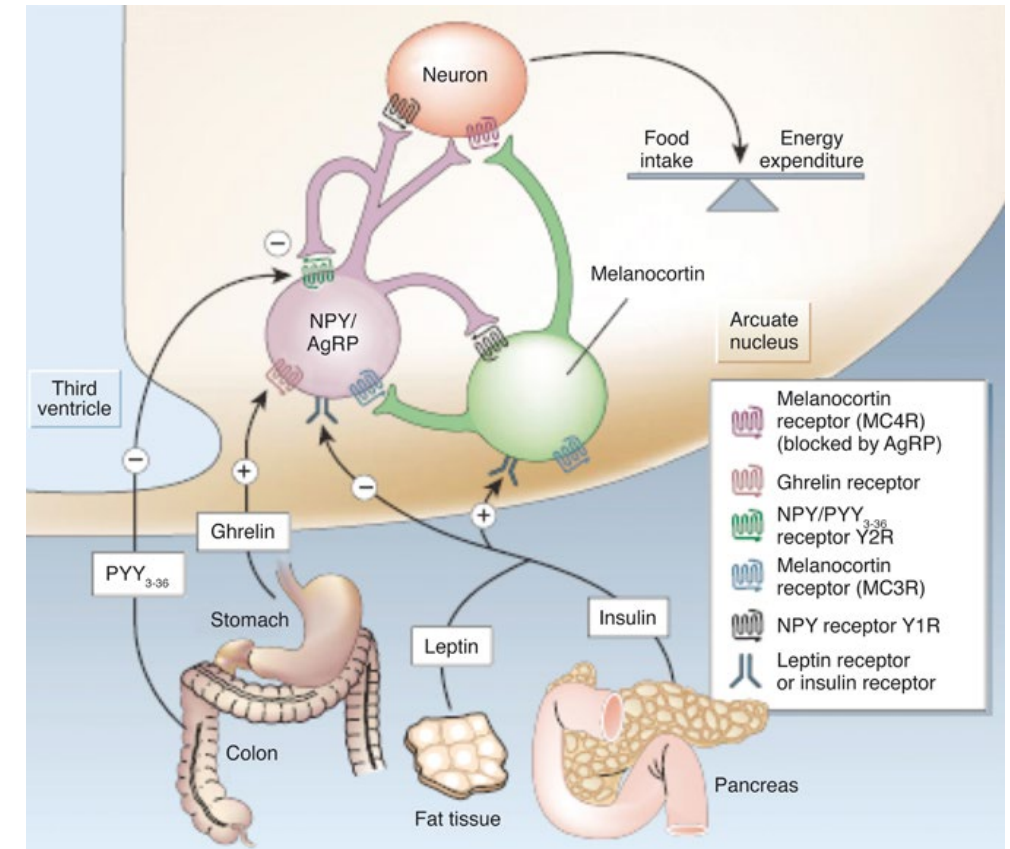
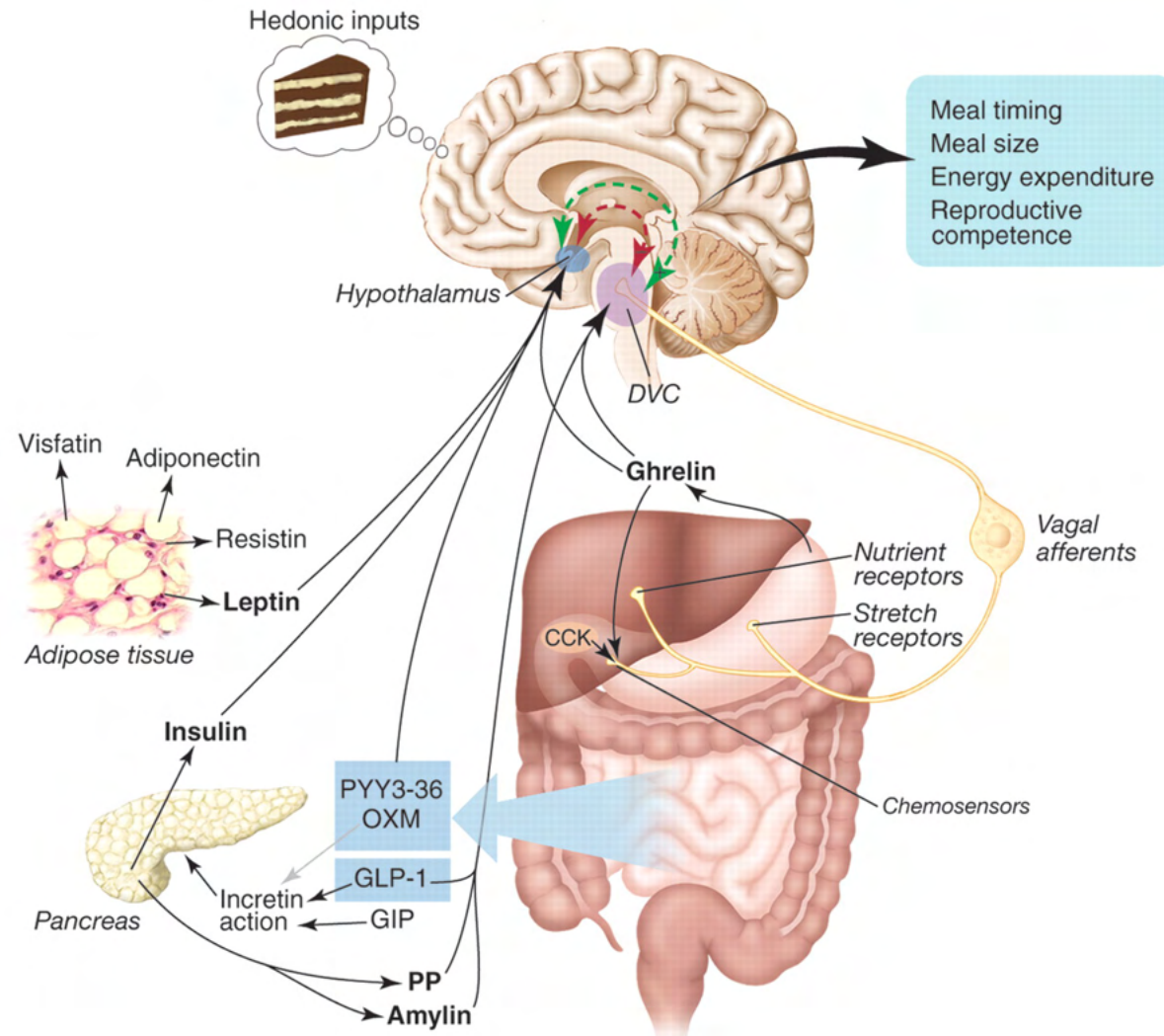
LeRoux CW et al. Endocrinology 2006;147:3-8

Obesity is a chronic disease



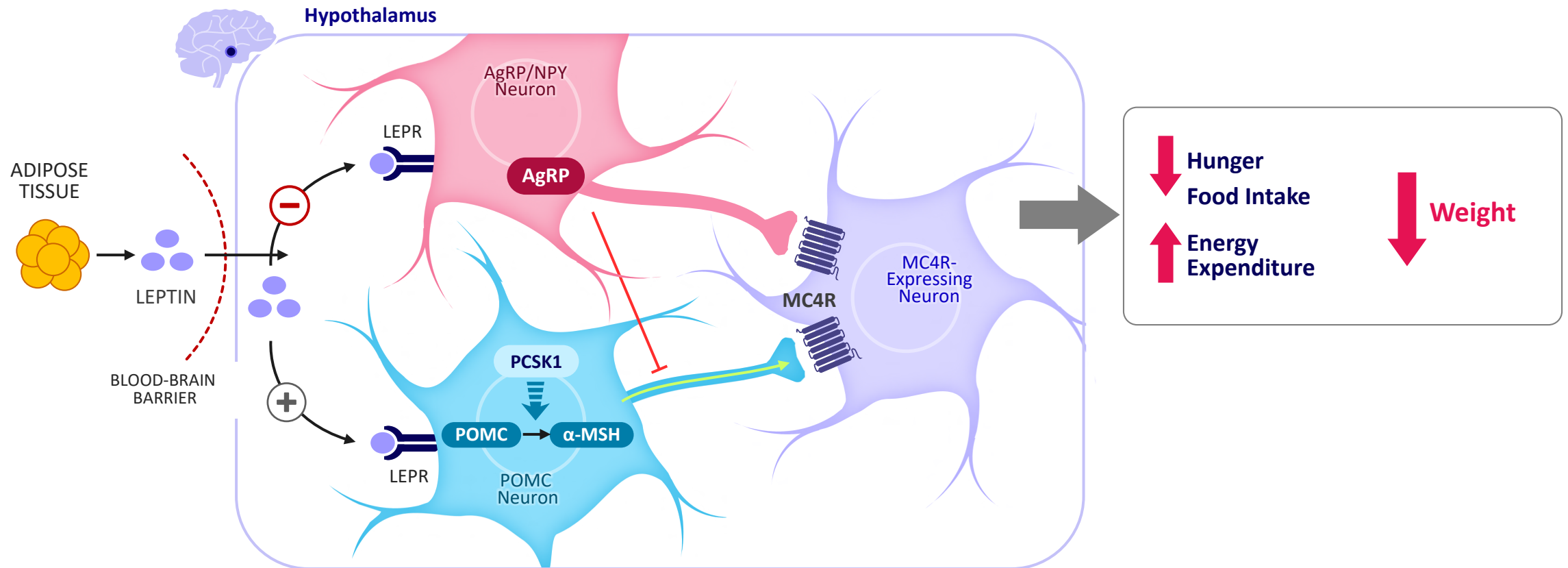
Badman & Flier. Science 2005

Obesity is a chronic disease



Badman & Flier. Science 2005

Obesity is a chronic disease



Obesity is a chronic disease

Genetics of Obesity: What We Have Learned Over Decades of Research

TABLE 2 Examples of single-gene defects responsible for human Mendelian obesity cases

Gene	Mutation type	Prevalence	Associated phenotypes
<i>Leptin</i>	Autosomal recessive inheritance	<100 patients worldwide	Hyperphagia Gonadotropic and thyrotrophic insufficiency Alteration in immune function
<i>LEPR</i>	Autosomal recessive inheritance	<3% of patients with severe early-onset obesity	Hyperphagia Gonadotropic, thyrotrophic, and somatotropin insufficiency Alteration in immune function
<i>MC4R</i>	Heterozygous or homozygous loss of function	About 5% of children with severe obesity, 1% of adults with severe obesity, and 0.1% of the general population	Hyperphagia Hyperinsulinemia High lean mass and bone mineral density
<i>NTK2</i>	Heterozygous missense mutation	<10 patients worldwide	Hyperphagia Developmental delay Behavioral disturbance Blunted response to pain
<i>PCSK1</i>	Autosomal recessive inheritance or compound heterozygotes	<20 patients worldwide	Hyperphagia Adrenal, gonadotropic, somatotropin, and thyrotrophic insufficiency Postprandial hypoglycemia
<i>POMC</i>	Autosomal recessive inheritance or compound heterozygotes	<10 patients worldwide	ACTH insufficiency Mild hypothyroidism Pale skin and red hair in Caucasian individuals
<i>SIM1</i>	Translocation between chromosome 1p22.1 and 6q16.2 or dominant inheritance	<50 patients worldwide	Neurobehavioral abnormalities Memory deficit, emotional lability, or autism-like behavior

Modified and amplified from Huvenne et al. (88).
ACTH, adrenocorticotrophic hormone.

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Two Key Clinical Characteristics Can Suggest the Presence of a Rare Genetic Disease of Obesity



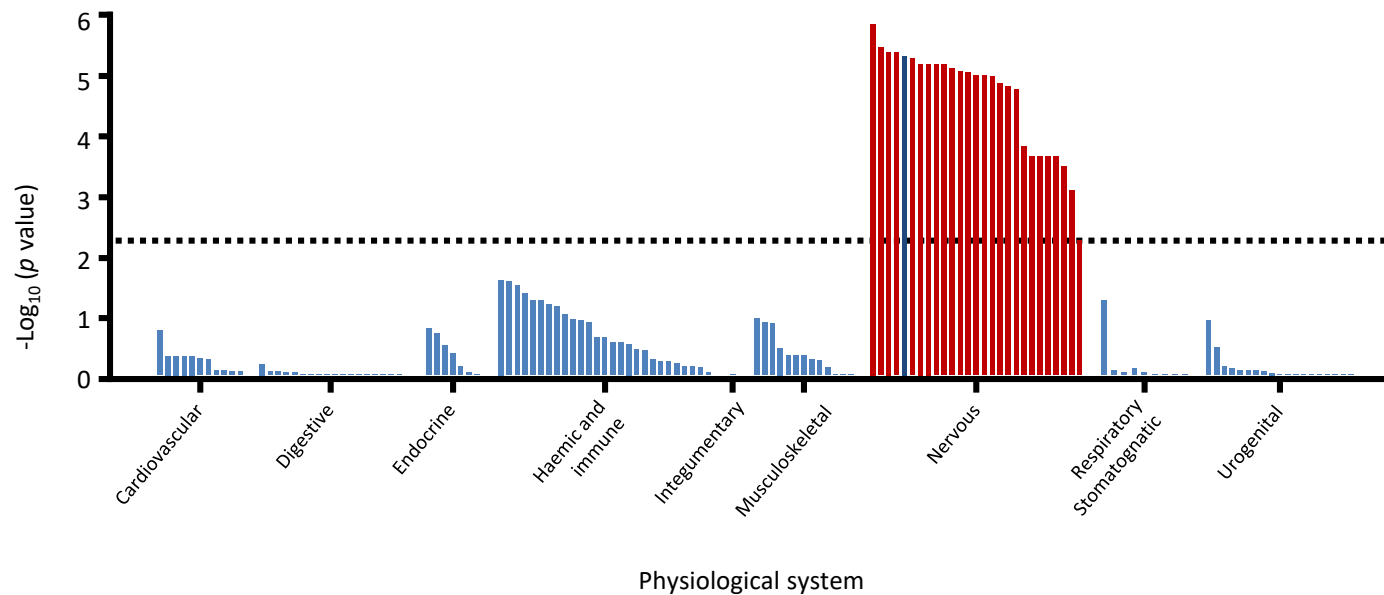
Hyperphagia
(insatiable hunger)



**Early-onset,
severe obesity**

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Tissues sorted by physiological system – genes from CNS showed association

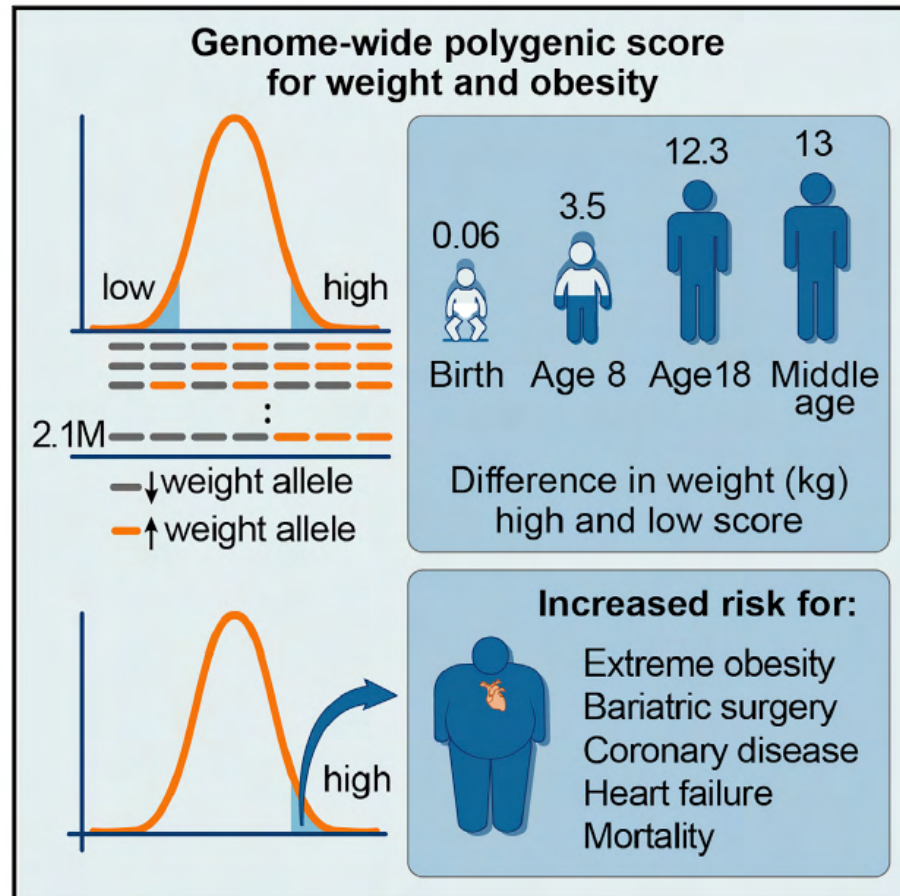


CNS, central nervous system; GWAS, Genome-Wide Association Study

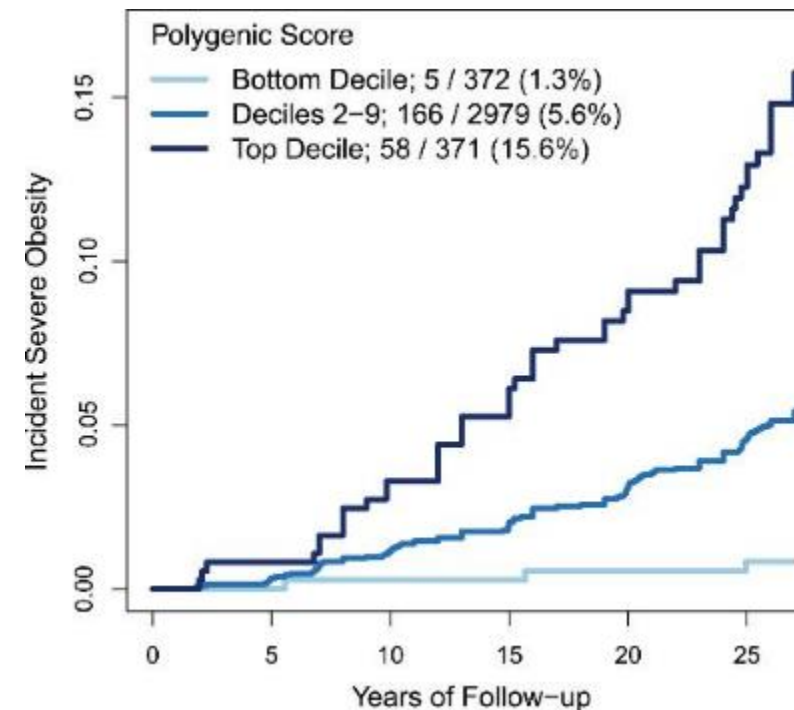
Locke AE *et al.* *Nature* 2015;518:197–206

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Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood



A genome-wide polygenic score quantifies inherited susceptibility to obesity, integrating information from 2.1 million common genetic variants to identify adults at risk of severe obesity.



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Environmental Drivers to Obesity

(3) Stress and distress

(direct impact on relevant areas of the brain)

(4) Drugs

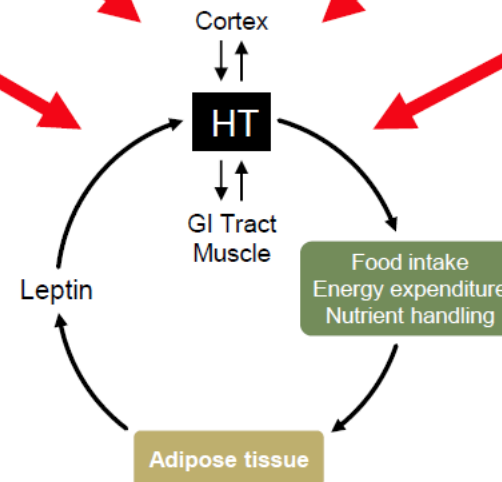
(accounts for up to 10%)

(2) Decreased physical activity

(effects on muscle more than calories)

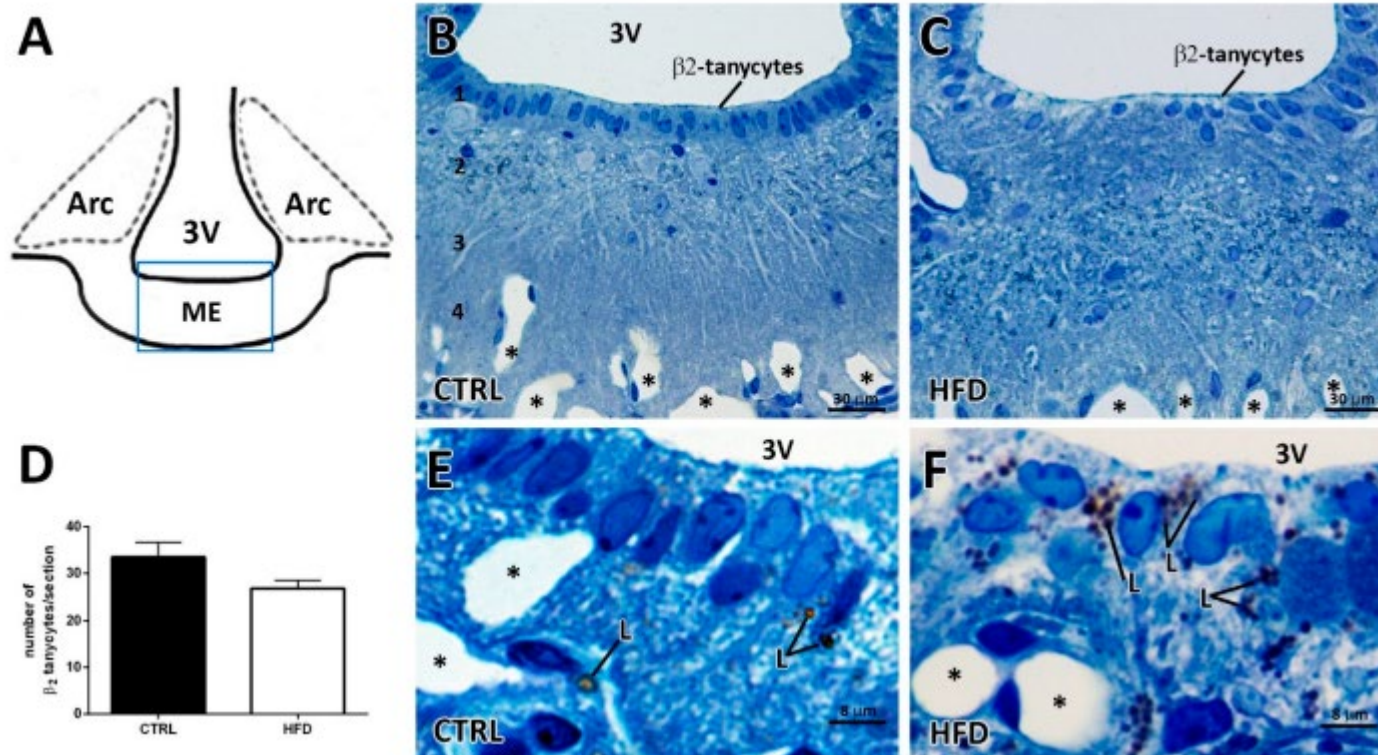
(1) Altered food supply

(signaling more than calories)

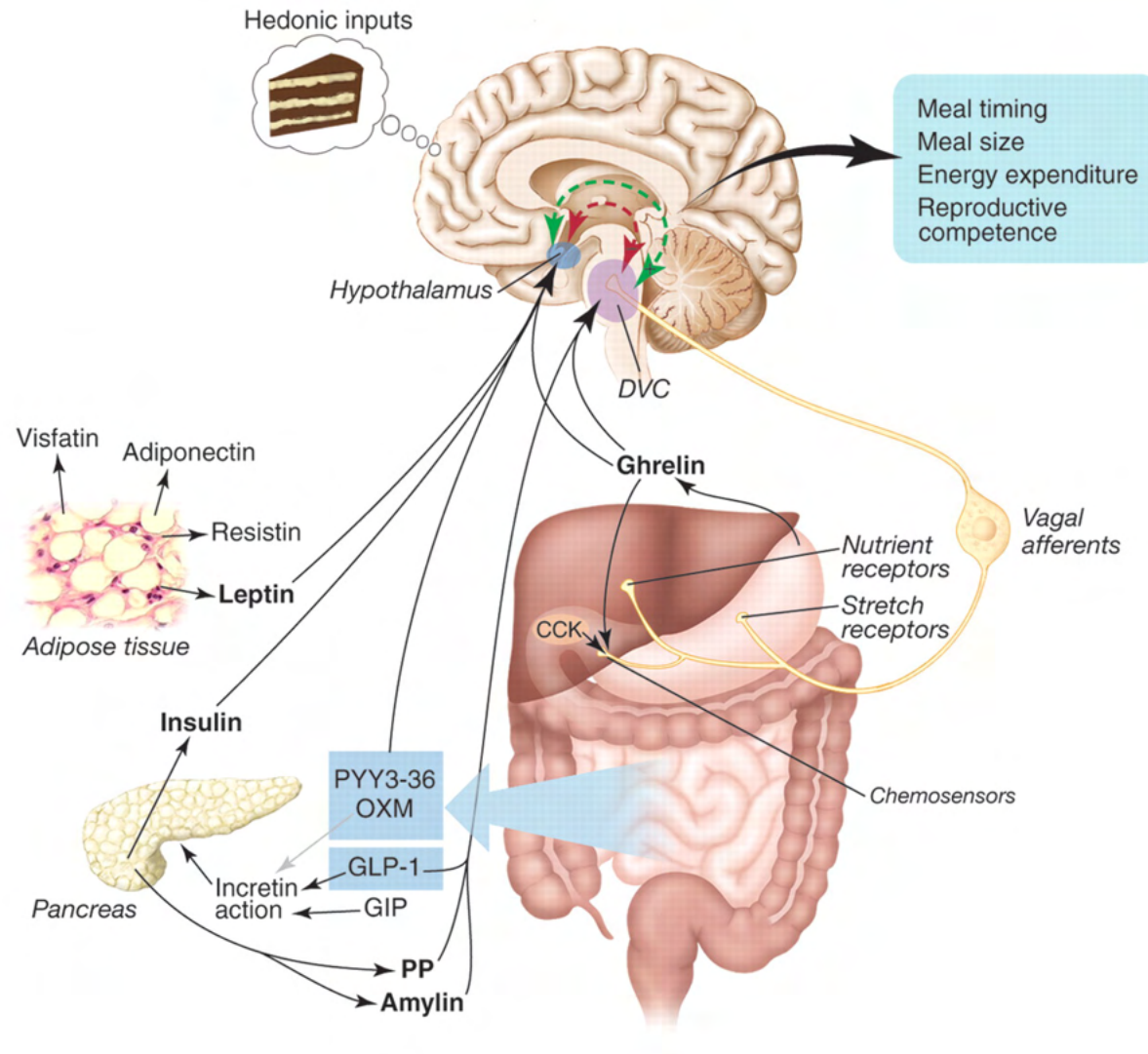


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High-Fat Diet Impairs Mouse Median Eminence: A Study by Transmission and Scanning Electron Microscopy Coupled with Raman Spectroscopy

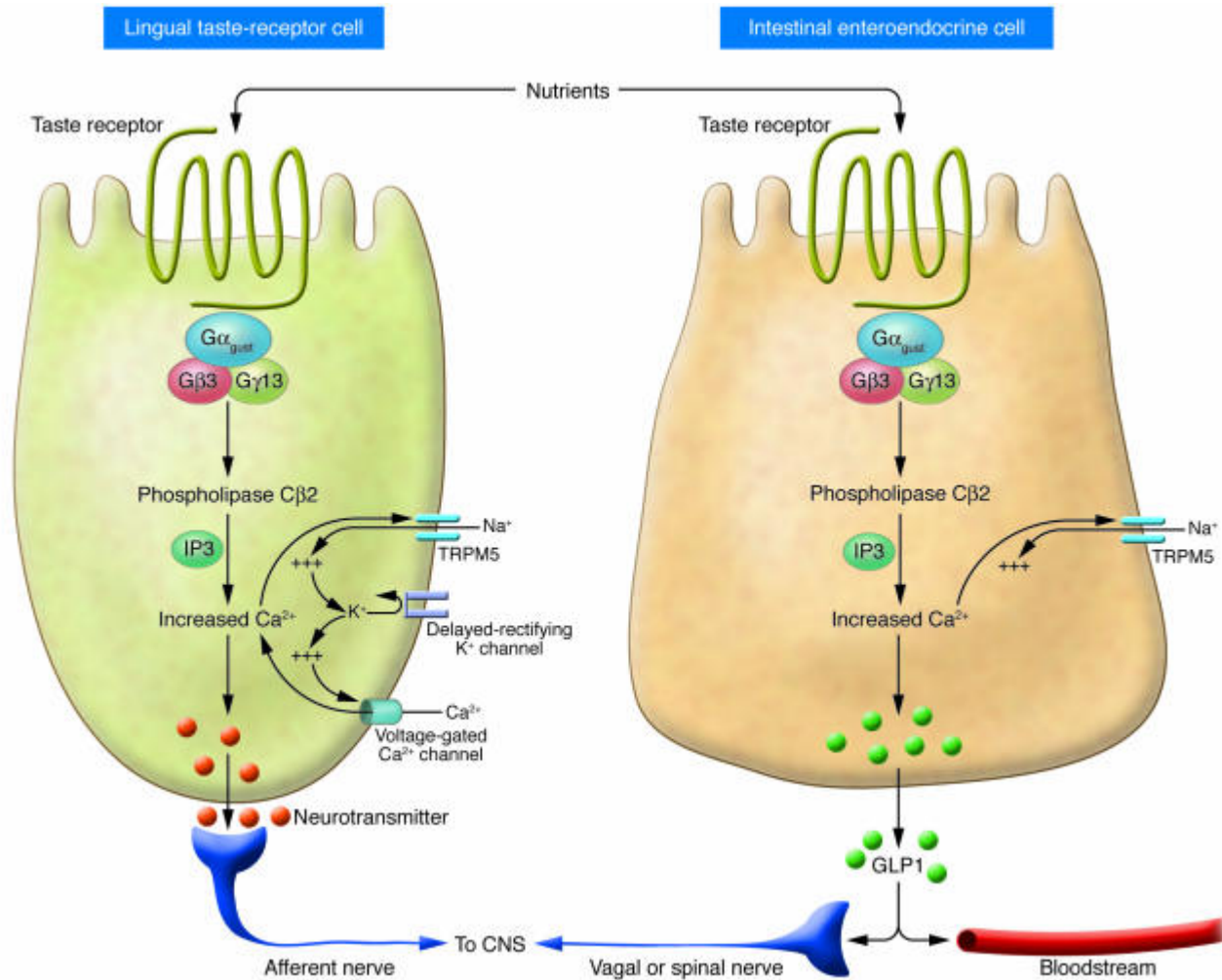


Obesity is a chronic disease



Badman & Flier. Science 2005

Obesity is a chronic disease



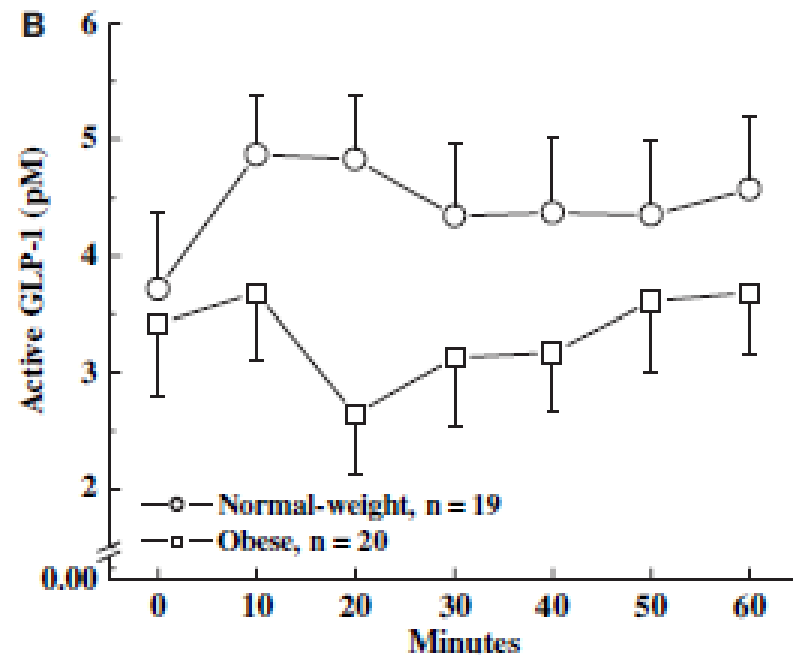
Gastrointestinal regulation of food intake

David E. Cummings and Joost Overduin

The Journal of Clinical Investigation January 2007

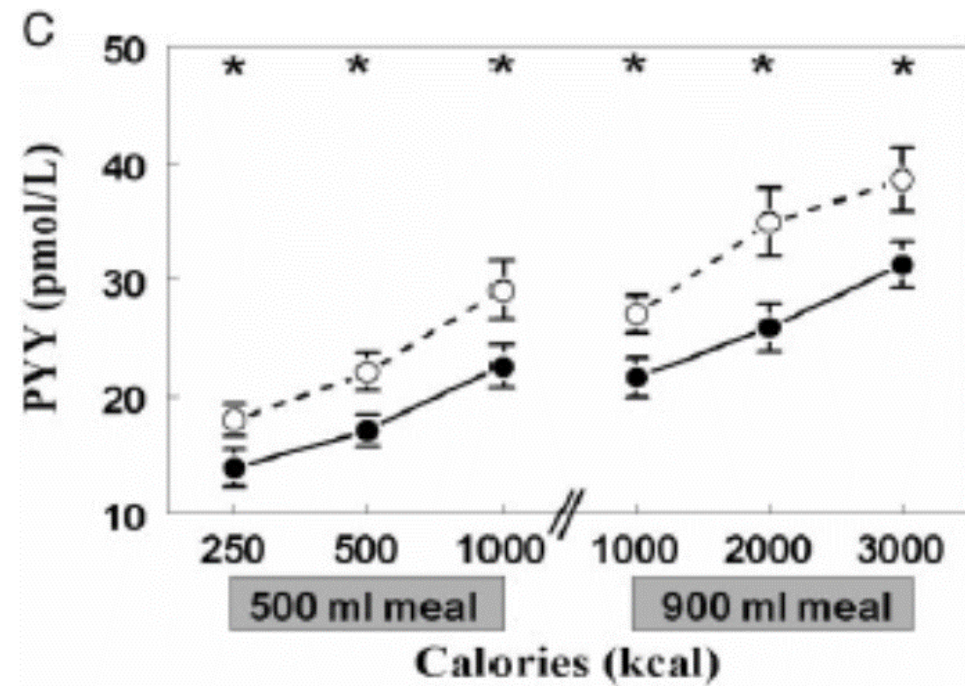
Obesity is a chronic disease

Influence of BMI on post-prandial GLP-1 response



Carroll JF et al. Obesity 2007;15:2974

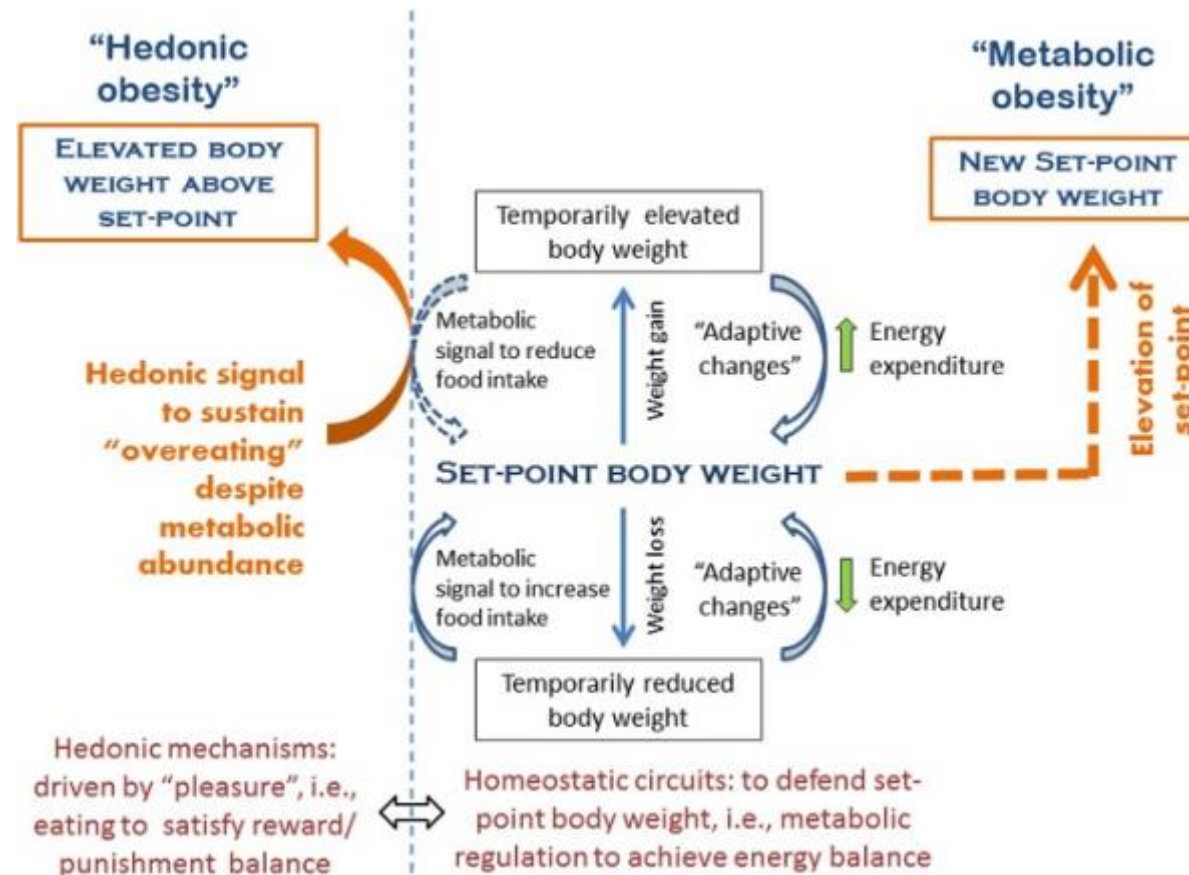
Attenuated Peptide YY Release in Obese Subjects Is Associated with Reduced Satiety



LeRoux CW et al. Endocrinology 2006;147:3

Obesity is a chronic disease

Metabolic vs. hedonic obesity: a conceptual distinction and its clinical implications



Obesity is a chronic disease

Neural responses to visual food cues according to weight status: a systematic review of functional magnetic resonance imaging studies

Sixty studies were identified that investigated the neural responses of healthy weight participants ($n = 26$), healthy weight compared to obese participants ($n = 17$), and weight-loss interventions ($n = 12$). High-calorie food images were used in the majority of studies ($n = 36$).

- Obese individuals had increased activation of reward-related brain areas including the insula and orbitofrontal cortex in response to visual food cues compared to healthy weight individuals
- This was particularly evident in response to energy dense cues.
- Additionally, obese individuals were more responsive to food images when satiated.

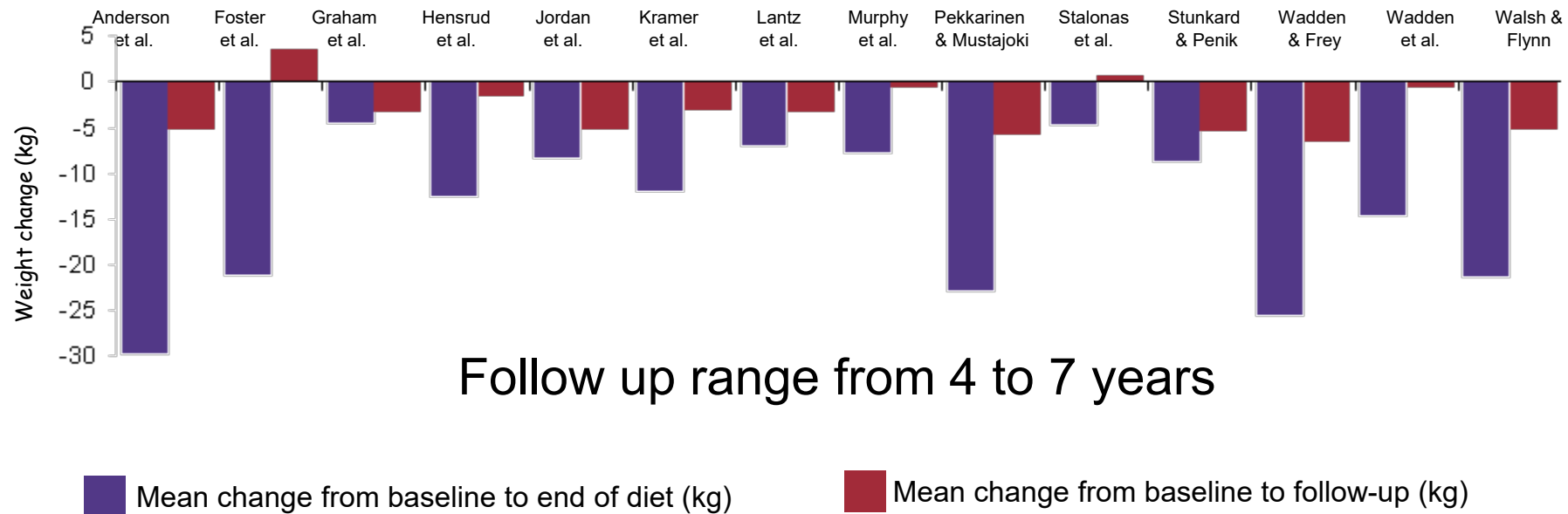
Obesity is a relapsing disease

World Obesity Federation Position Statement

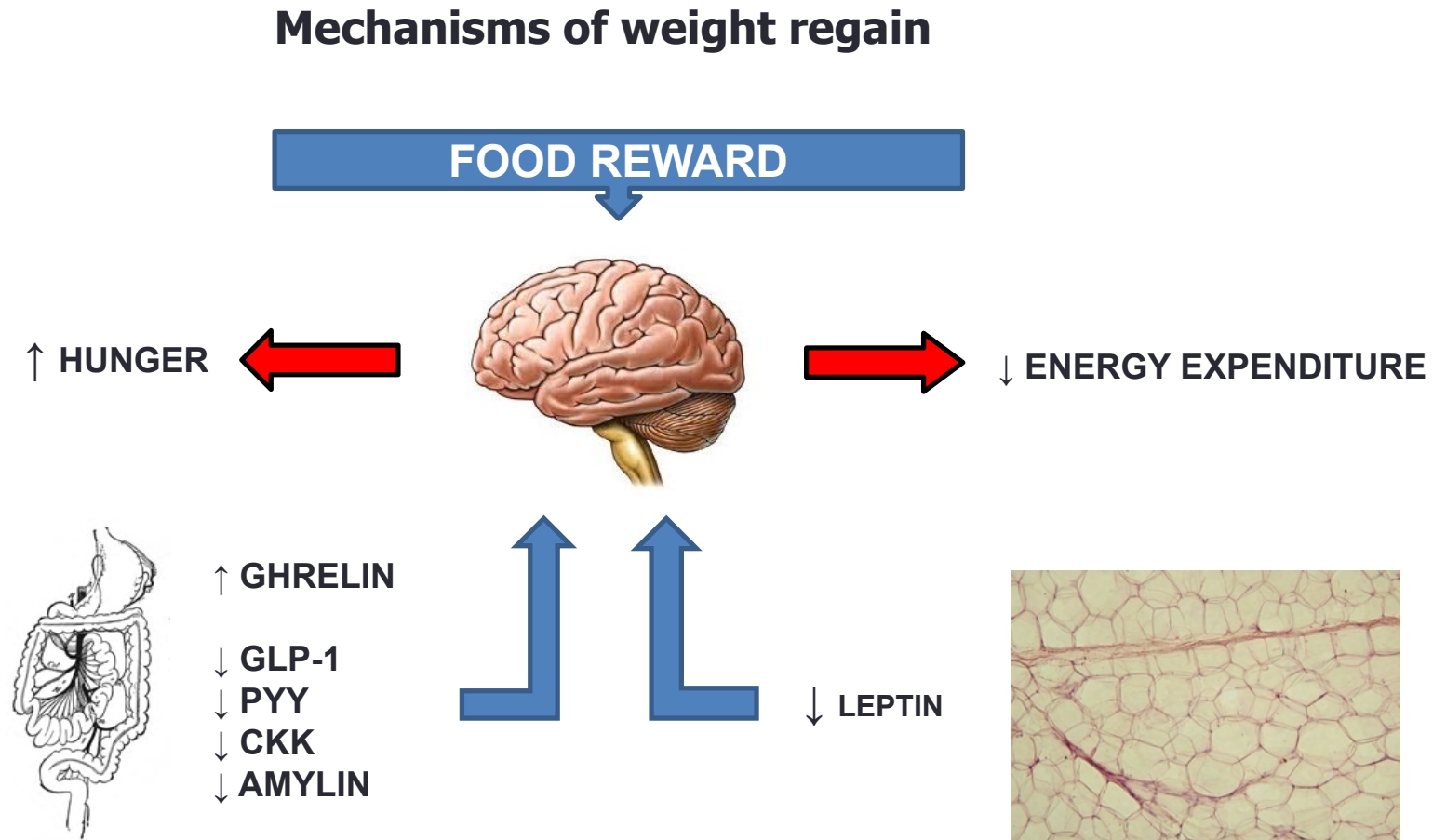
Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation

Obesity is a relapsing disease

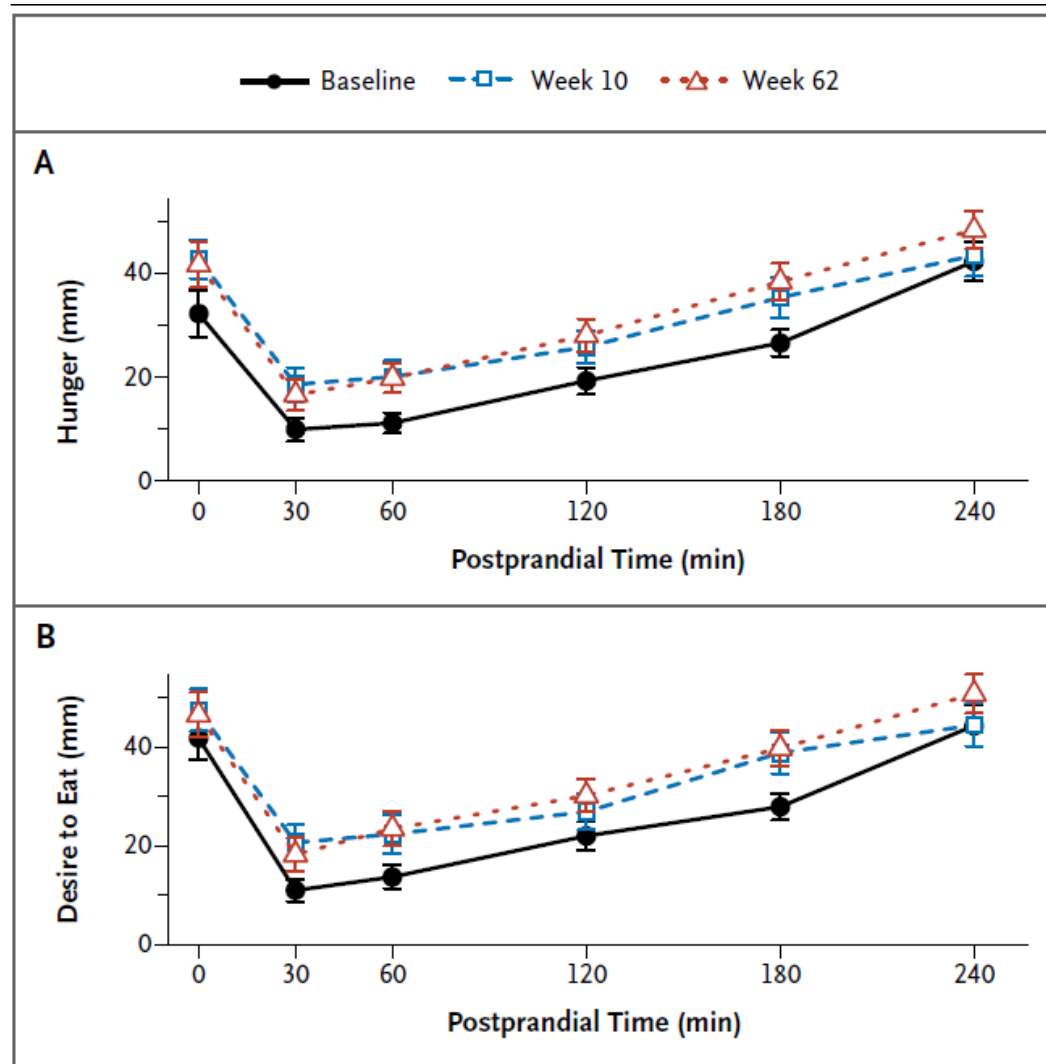
WEIGHT MAINTENANCE IS THE MOST RELEVANT PROBLEM IN OBESITY MANAGEMENT



Obesity is a relapsing disease



Obesity is a relapsing disease

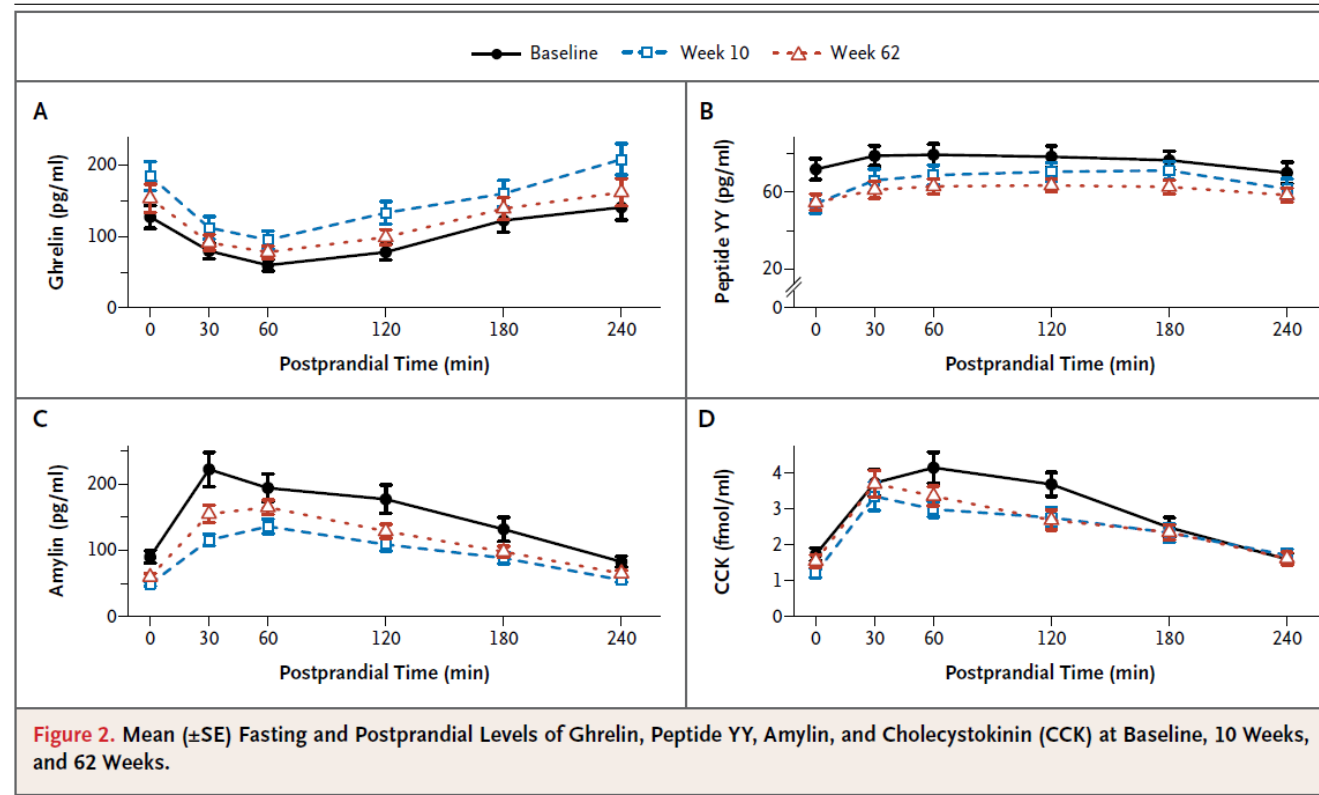


Long-Term Persistence of Hormonal Adaptations to Weight Loss

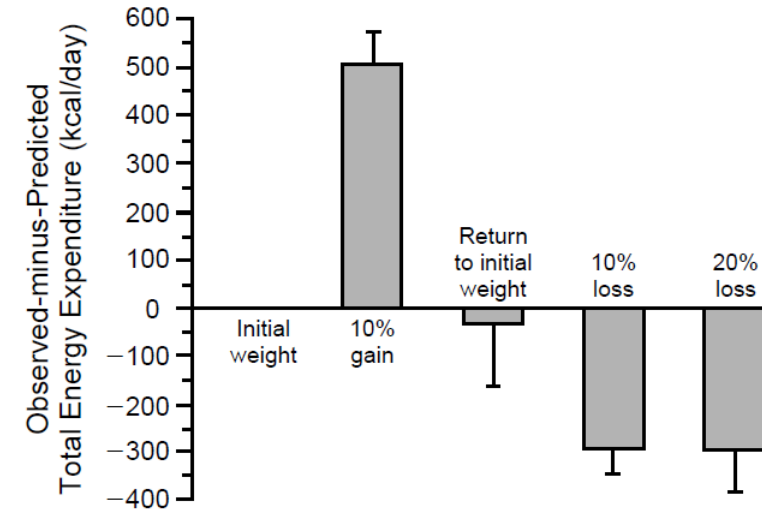
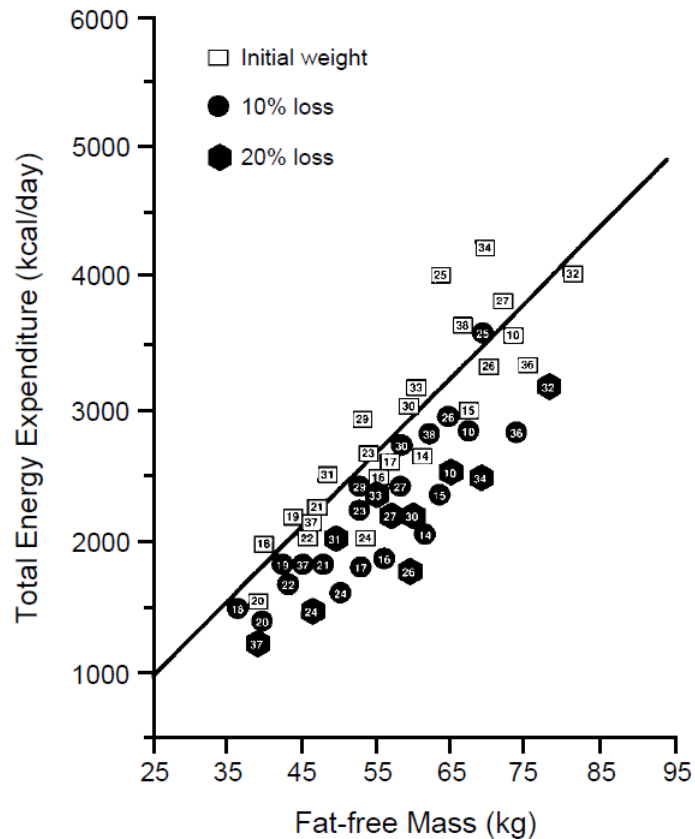
Sumithran P et al. N Engl J Med 2011;365:1597

Obesity is a relapsing disease

Long-Term Persistence of Hormonal Adaptations to Weight Loss



Obesity is a relapsing disease



Metabolic Adaptation

A reduction in basal metabolism rate not accounted for the changes in either body mass or body mass components occurring with weight loss

Leibell RL et al. New Engl J Med 1995;332:621

Obesity is a relapsing disease

Modifications of Resting Energy Expenditure After Sleeve Gastrectomy

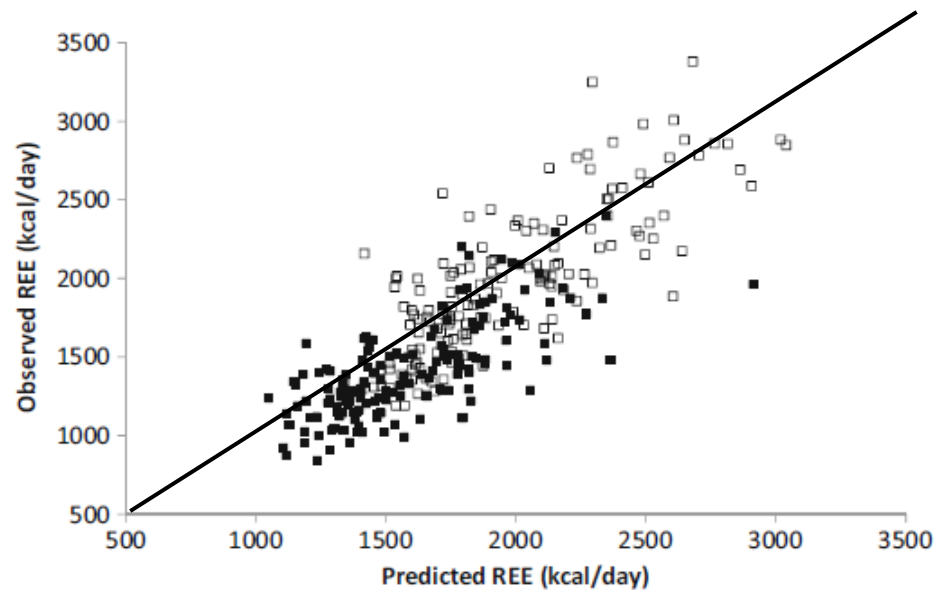


Fig. 1 Distribution of the predicted and observed REE values before (open symbols) and 12 months after sleeve gastrectomy (closed symbols). Most of the observed post-surgery REE values are distributed below the identity line, confirming the existence of a certain degree of metabolic adaptation

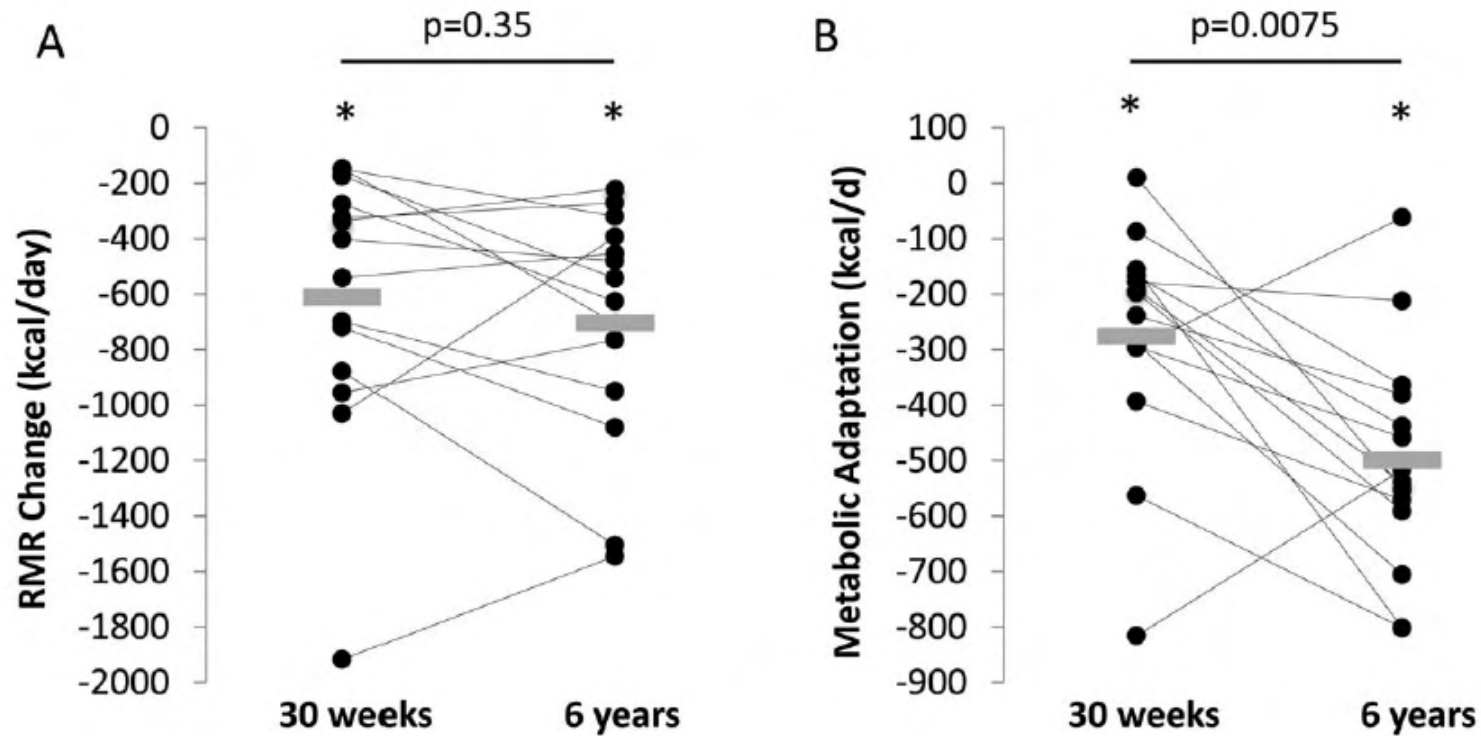
METABOLIC ADAPTATION

- 199 ± 238 kcal/day

Moreover, the level of metabolic adaptation after surgery was inversely related to postoperative percent weight loss ($r = -0.170$; $P < 0.05$) and FM loss ($r = -0.245$; $P < 0.01$).



Obesity is a relapsing disease

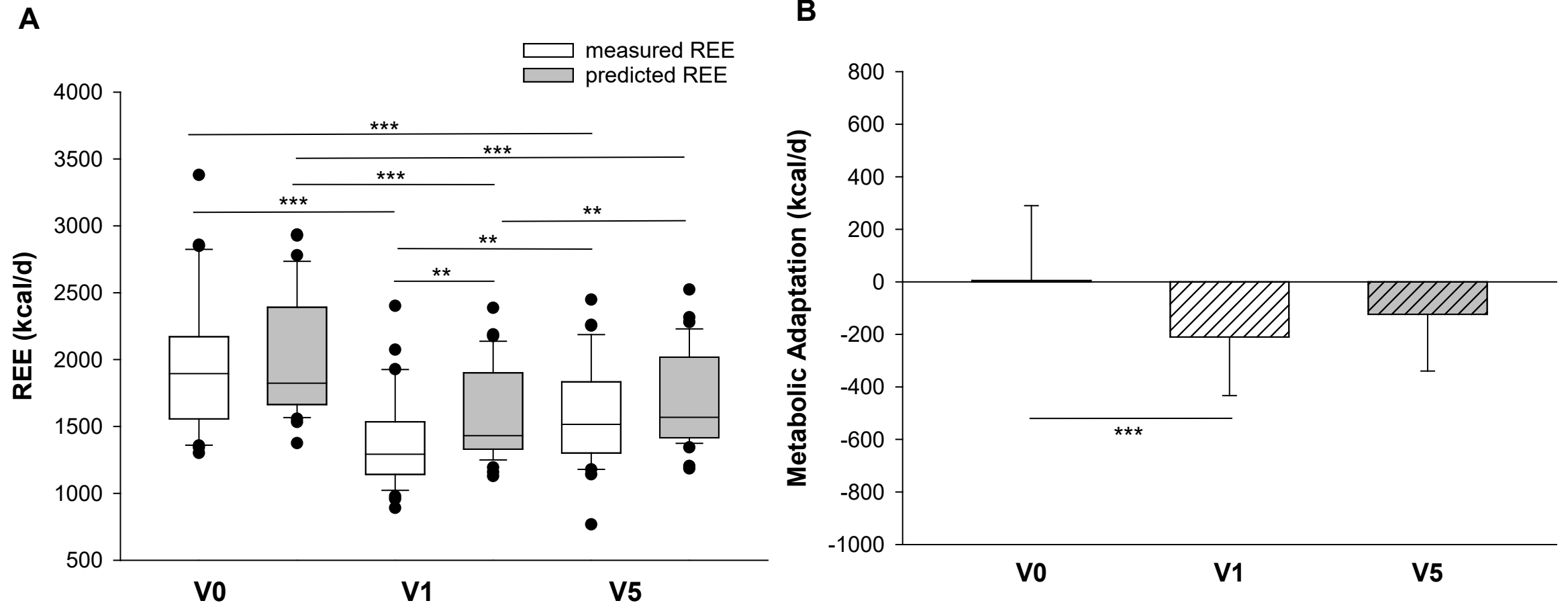


“The Biggest Loser” competition



Fothergill et al. Obesity 2016;24:1612-9

Obesity is a relapsing disease



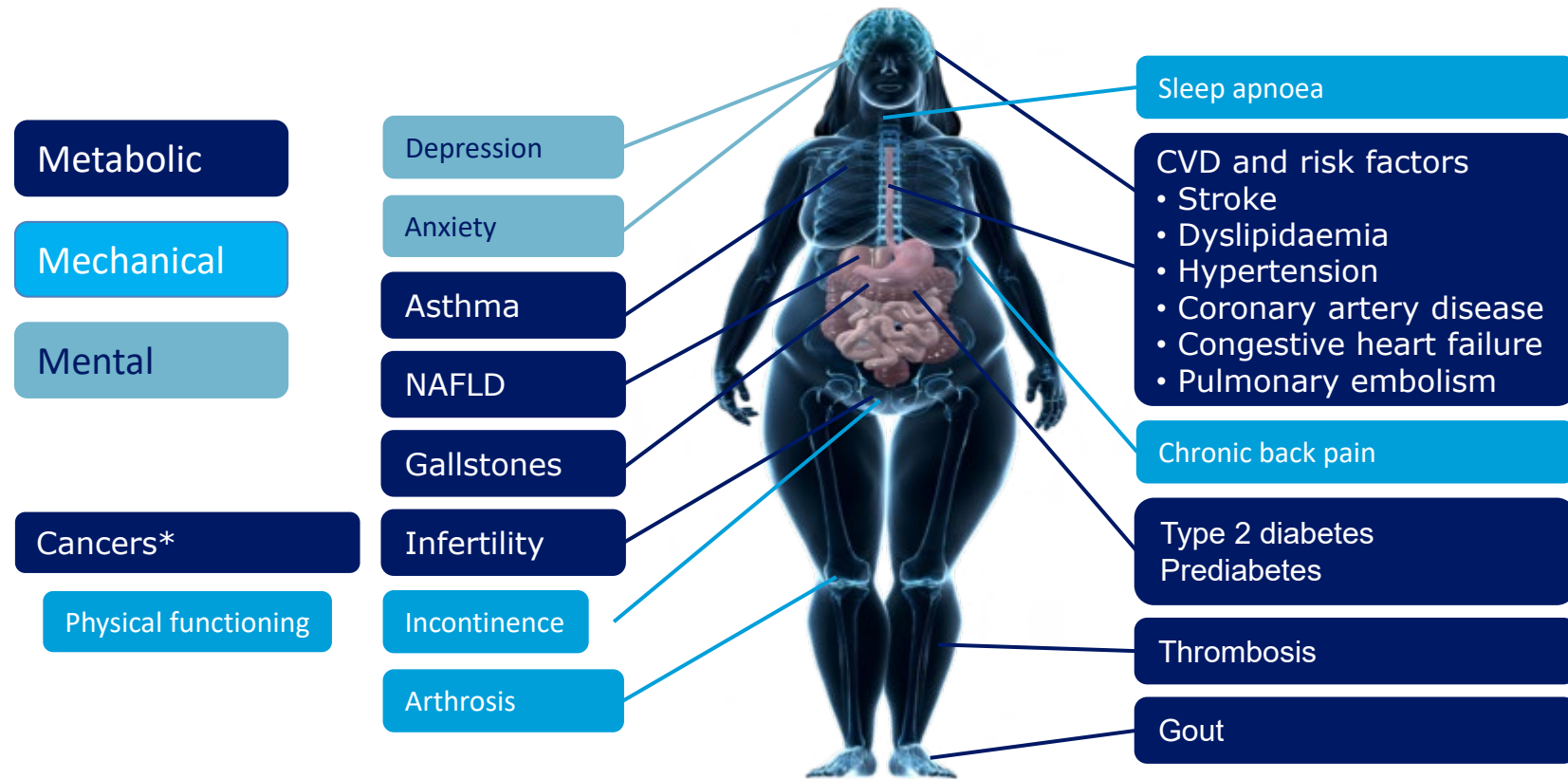
Bettini S et al. J Clin Endocrinol Metab 2022, June 1st

Obesity is a relapsing disease

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Obesity is a progressive disease

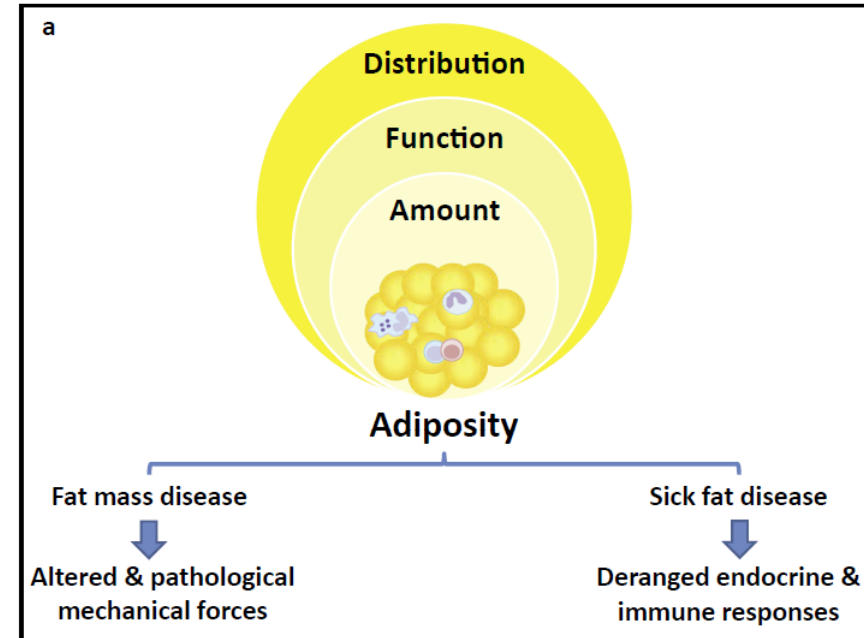


Obesity is a progressive disease

The ABCD of Obesity: An EASO Position Statement on a Diagnostic Term with Clinical and Scientific Implications

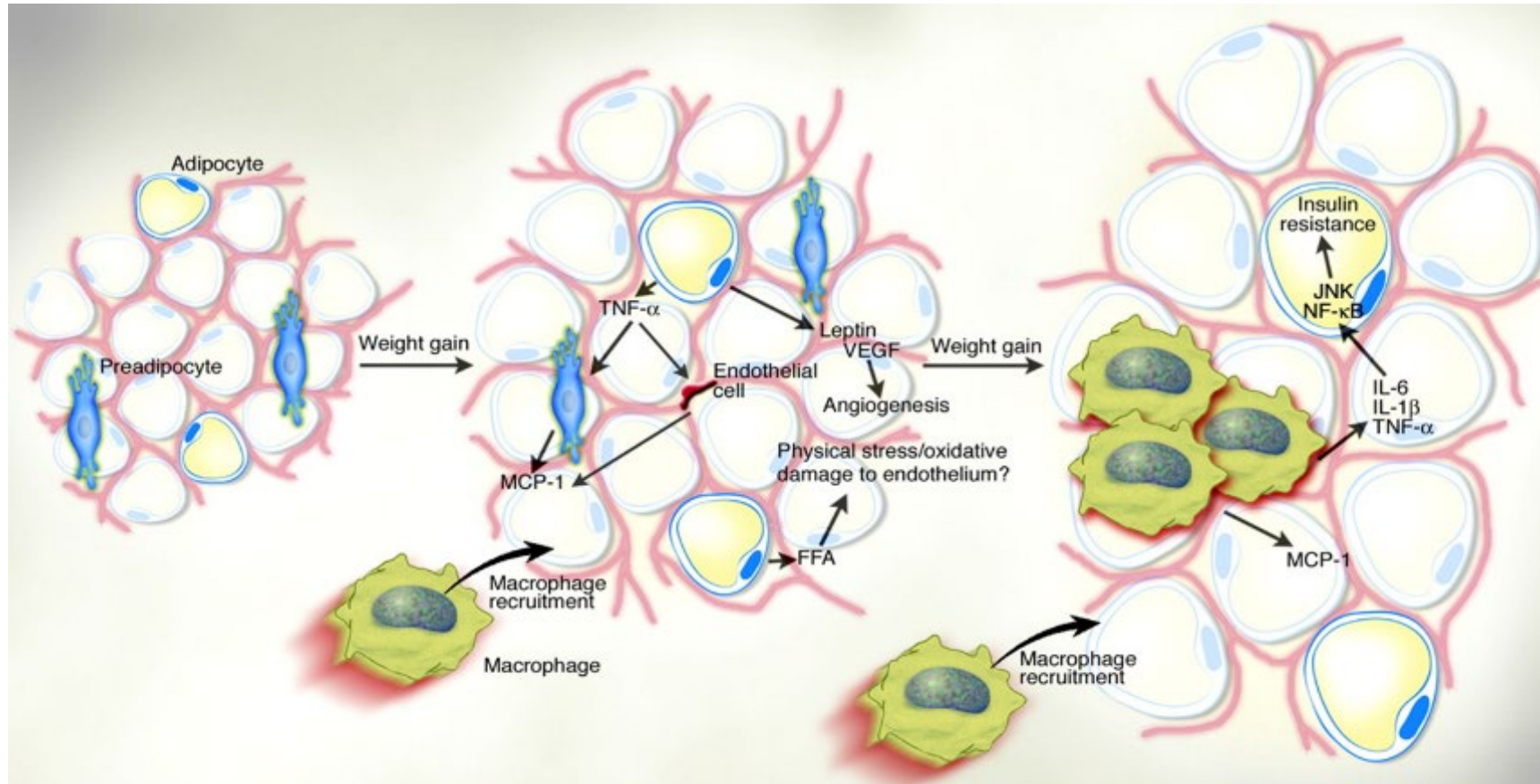
Gema Frühbeck^{a, b} Luca Busetto^{a, c} Dror Dicker^{a, d} Volkan Yumuk^{a, e}
Gijs H. Goossens^{a, f} Johannes Hebebrand^{a, g} Jason G.C. Halford^{a, h}
Nathalie J. Farpour-Lambert^{a, i} Ellen E. Blaak^{a, f} Euan Woodward^{a, j}
Hermann Toplak^{a, k}

Obesity Facts
The European Journal of Obesity



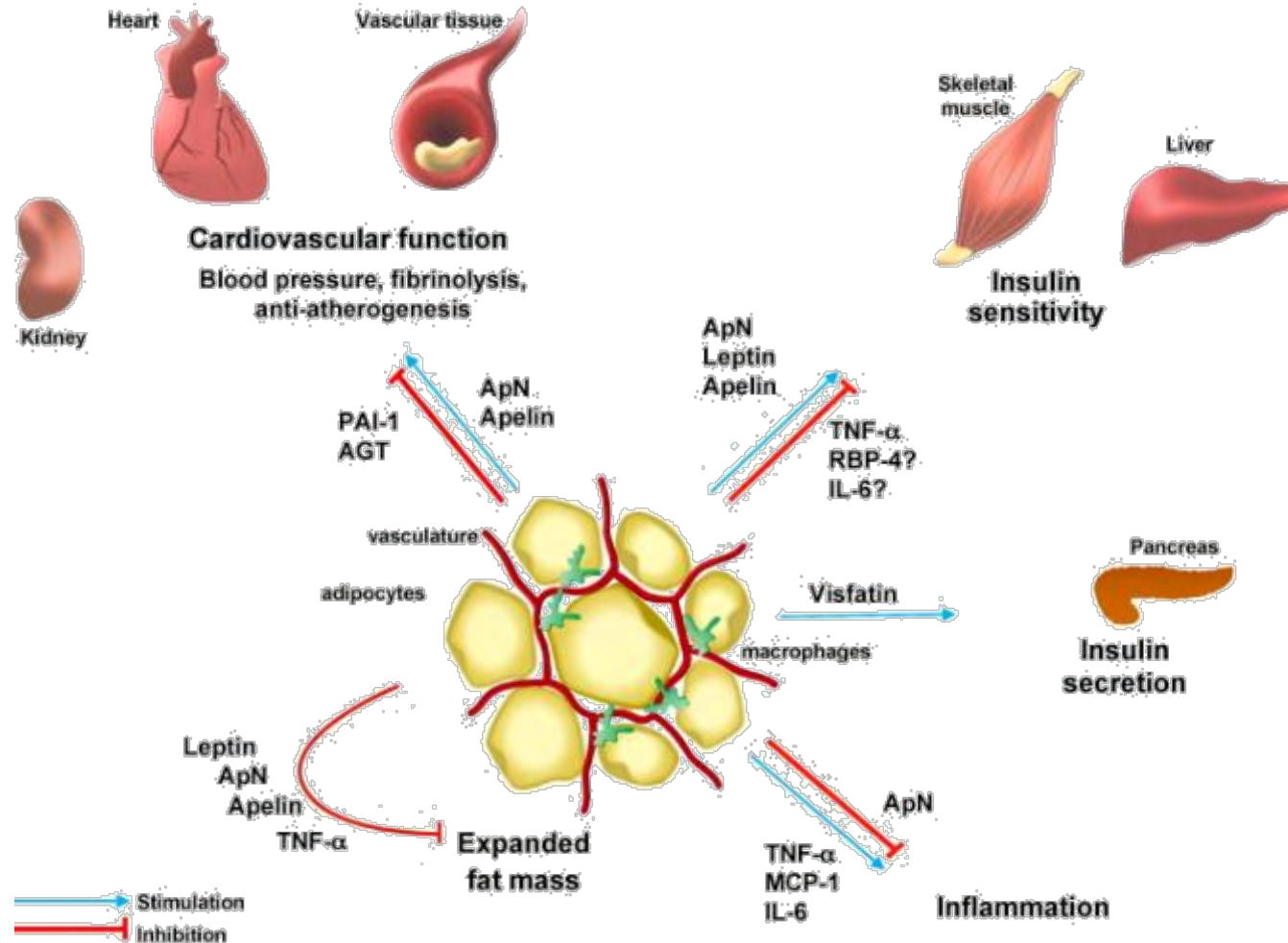
Frühbeck G et al. *Obes Facts* 2019;12:131

Obesity is a progressive disease



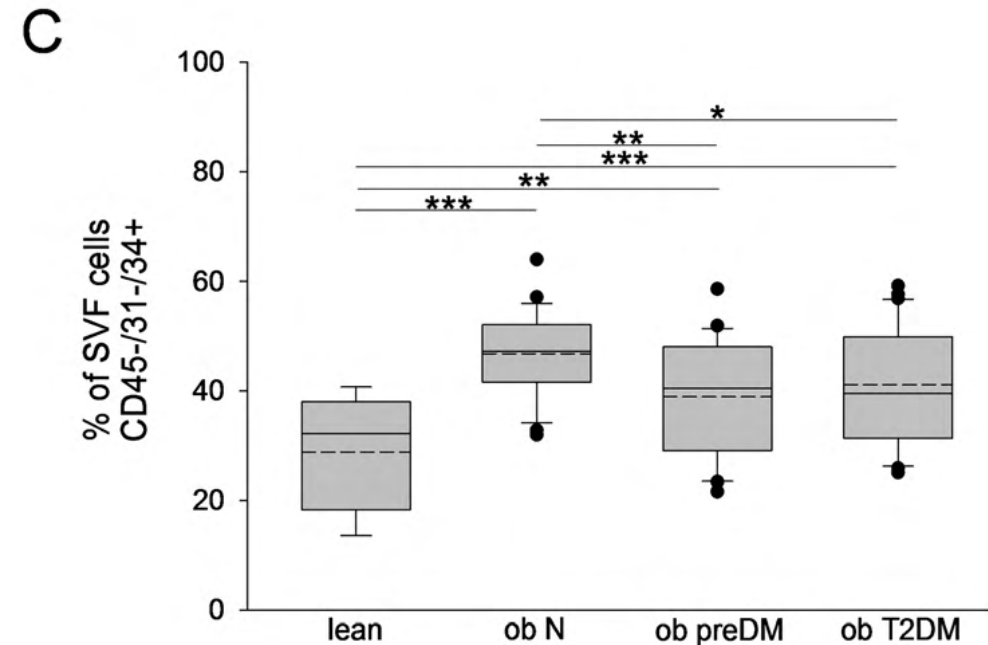
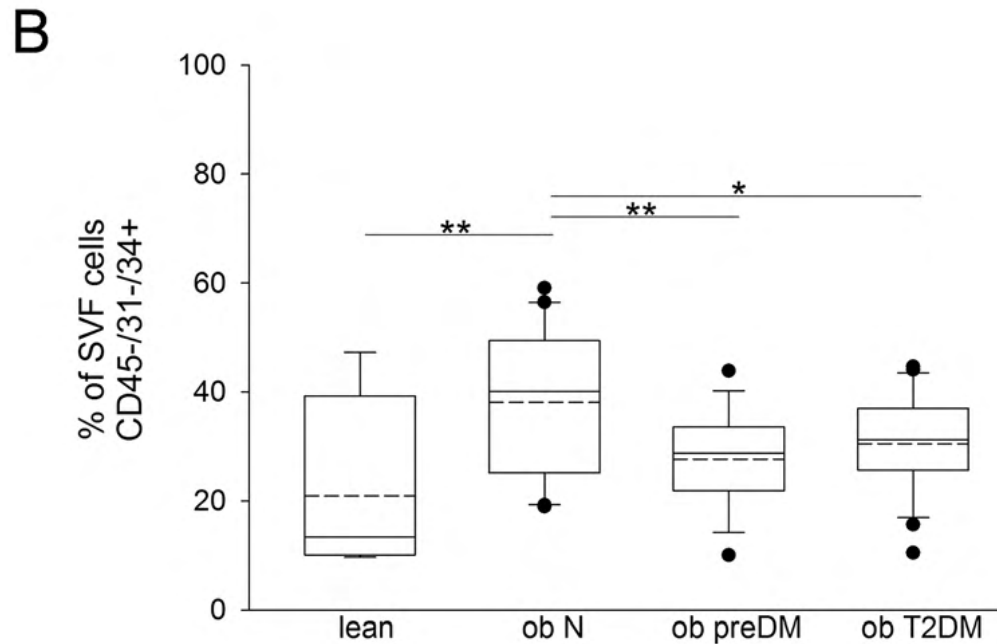
Wellen KE et al. J Clin Invest 2003;112:1785

Obesity is a progressive disease

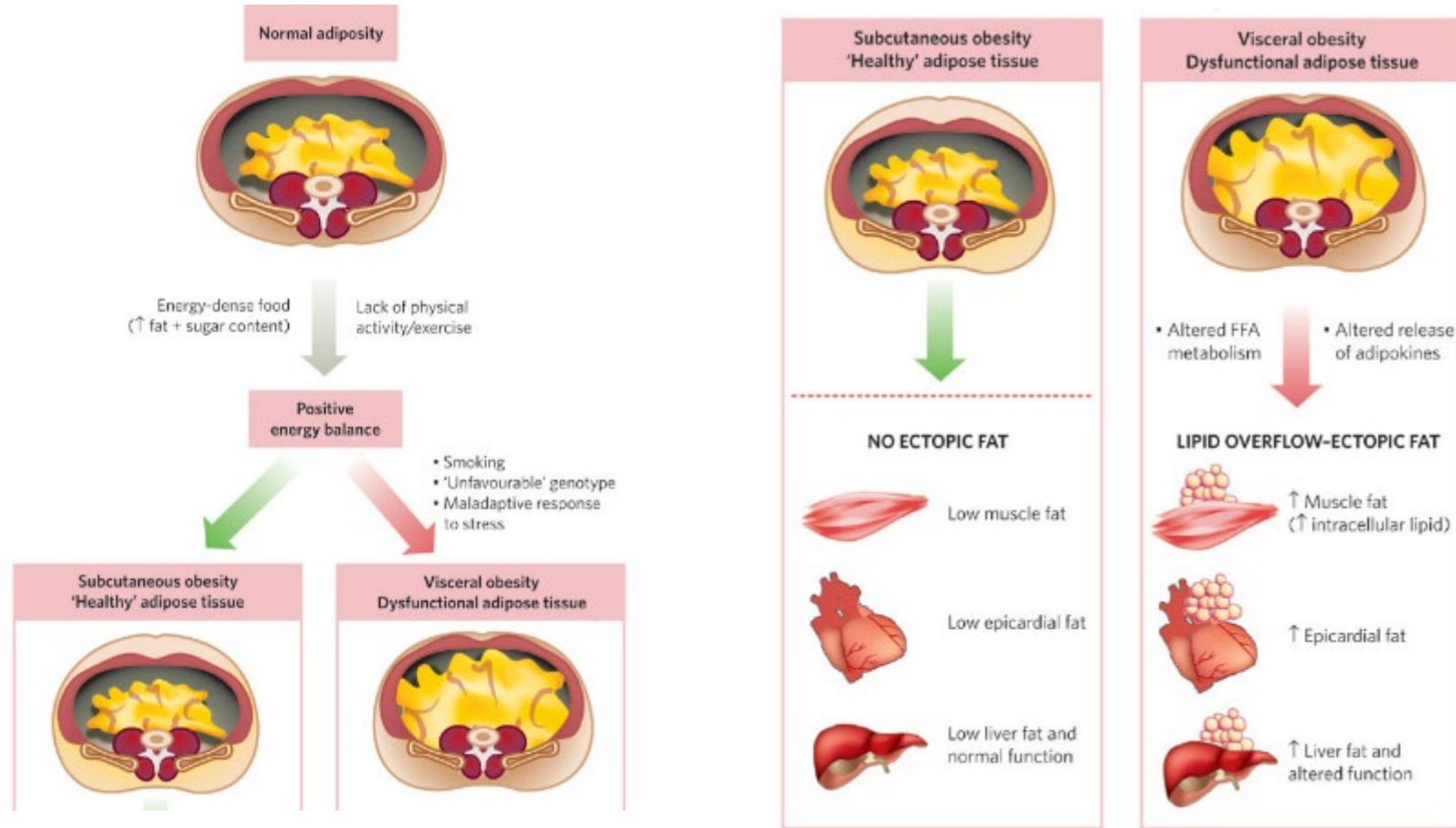


Obesity is a progressive disease

Characterization of subcutaneous and omental adipose tissue in patients with obesity and with different degrees of glucose impairment



Obesity is a progressive disease



Obesity is a progressive disease

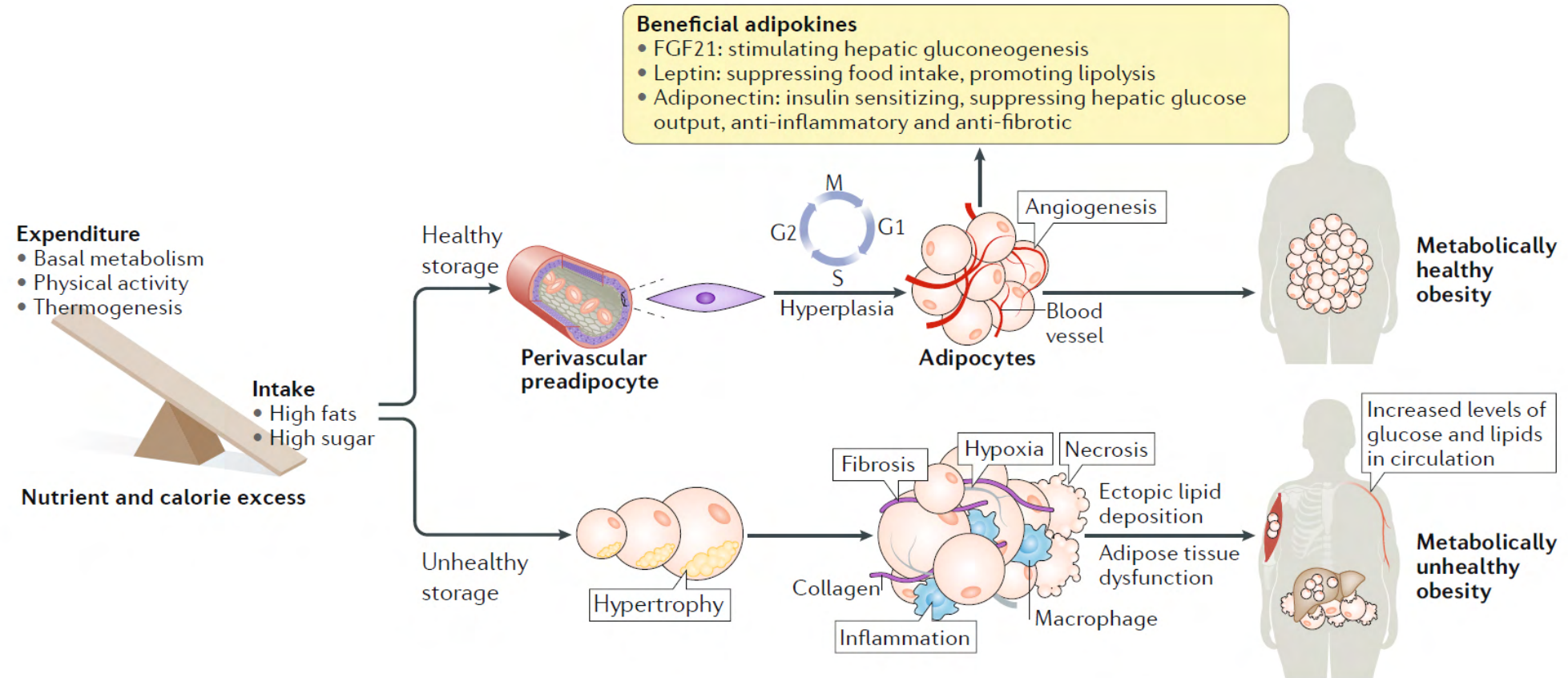


Figure 5. Diagnosis and Medical Management of Obesity

DIAGNOSIS		COMPLICATION-SPECIFIC STAGING AND TREATMENT		
Anthropometric Component (BMI kg/m ²)	Clinical Component	Disease Stage	Chronic Disease Phase of Prevention	Suggested Therapy (based on clinical judgment)
				
<25 <23 in certain ethnicities waist circumference below regional/ethnic cutoffs		Normal weight (no obesity)	Primary	• Healthy lifestyle: healthy meal plan/physical activity
25–29.9 23–24.9 in certain ethnicities	Evaluate for presence or absence of adiposity-related complications and severity of complications	Overweight stage 0 (no complications)	Secondary	• Lifestyle therapy: Reduced-calorie healthy meal plan/physical activity/behavioral interventions
≥30 ≥25 in certain ethnicities	• Metabolic syndrome • Prediabetes • Type 2 diabetes • Dyslipidemia • Hypertension • Cardiovascular disease	Obesity stage 0 (no complications)	Secondary	• Lifestyle therapy: Reduced-calorie healthy meal plan/physical activity/behavioral interventions • Weight-loss medications: Consider after lifestyle therapy fails to prevent progressive weight gain. (BMI ≥27)
≥25 ≥23 in certain ethnicities	• Nonalcoholic fatty liver disease • Polycystic ovary syndrome • Female infertility • Male hypogonadism • Obstructive sleep apnea • Asthma/reactive airway disease	Obesity stage 1 (1 or more mild-moderate complications)	Tertiary	• Lifestyle therapy: Reduced-calorie healthy meal plan/physical activity/behavioral interventions • Weight-loss medications: Consider after lifestyle therapy fails to achieve therapeutic target or initiate concurrent with lifestyle therapy. (BMI ≥27)
≥25 ≥23 in certain ethnicities	• Osteoarthritis • Urinary stress incontinence • Gastroesophageal reflux disease • Depression	Obesity stage 2 (at least 1 severe complication)	Tertiary	• Lifestyle therapy: Reduced-calorie healthy meal plan/physical activity/behavioral interventions • Add weight-loss medication: Initiate concurrent with lifestyle therapy. (BMI ≥27) • Consider bariatric surgery: (BMI ≥35)

Obesity Staging

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AND AMERICAN COLLEGE OF ENDOCRINOLOGY
COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR
MEDICAL CARE OF PATIENTS WITH OBESITY**

ENDOCRINE PRACTICE Vol 22 (Suppl 3) July 2016

Obesity Staging

STAGE 0

- **NO** sign of obesity-related risk factors
- **NO** physical symptoms
- **NO** psychological symptoms
- **NO** functional limitations

Case Example:

Physically active female with a BMI of 32 kg/m², no risk factors, no physical symptoms, no self-esteem issues, and no functional limitations.

Class I, Stage 0 Obesity

EOSS Score

WHO Obesity Classification

STAGE 1

- Patient has obesity-related **SUBCLINICAL** risk factors (borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.) - **OR** -
- **MILD** physical symptoms - patient currently not requiring medical treatment for comorbidities (dyspnea on moderate exertion, occasional aches/pains, fatigue, etc.) - **OR** -
- **MILD** obesity-related psychological symptoms and/or mild impairment of well-being (quality of life not impacted)

Case Example:

38 year old female with a BMI of 59.2 kg/m², borderline hypertension, mild lower back pain, and knee pain. Patient does not require any medical intervention.

Class III, Stage 1 Obesity

STAGE 2

- Patient has **ESTABLISHED** obesity-related comorbidities requiring medical intervention (HTN, Type 2 Diabetes, sleep apnea, PCOS, osteoarthritis, reflux disease) - **OR** -
- **MODERATE** obesity-related psychological symptoms (depression, eating disorders, anxiety disorder) - **OR** -
- **MODERATE** functional limitations in daily activities (quality of life is beginning to be impacted)

Case Example:

32 year old male with a BMI of 36 kg/m² who has primary hypertension and obstructive sleep apnea.

Class II, Stage 2 Obesity

STAGE 3

- Patient has **significant** obesity-related end-organ damage (myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis) - **OR** -
- **SIGNIFICANT** obesity-related psychological symptoms (major depression, suicide ideation) - **OR** -
- **SIGNIFICANT** functional limitations (eg: unable to work or complete routine activities, reduced mobility)
- **SIGNIFICANT** impairment of well-being (quality of life is significantly impacted)

Case Example:

49 year old female with a BMI of 67 kg/m² diagnosed with sleep apnea, CV disease, GERD, and suffered from stroke. Patient's mobility is significantly limited due to osteoarthritis and gout.

Class III, Stage 3 Obesity

STAGE 4

- **SEVERE** (potential end stage) from obesity-related comorbidities - **OR** -
- **SEVERELY** disabling psychological symptoms - **OR** -
- **SEVERE** functional limitations

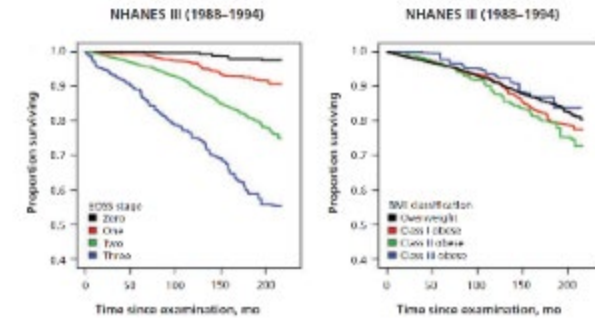
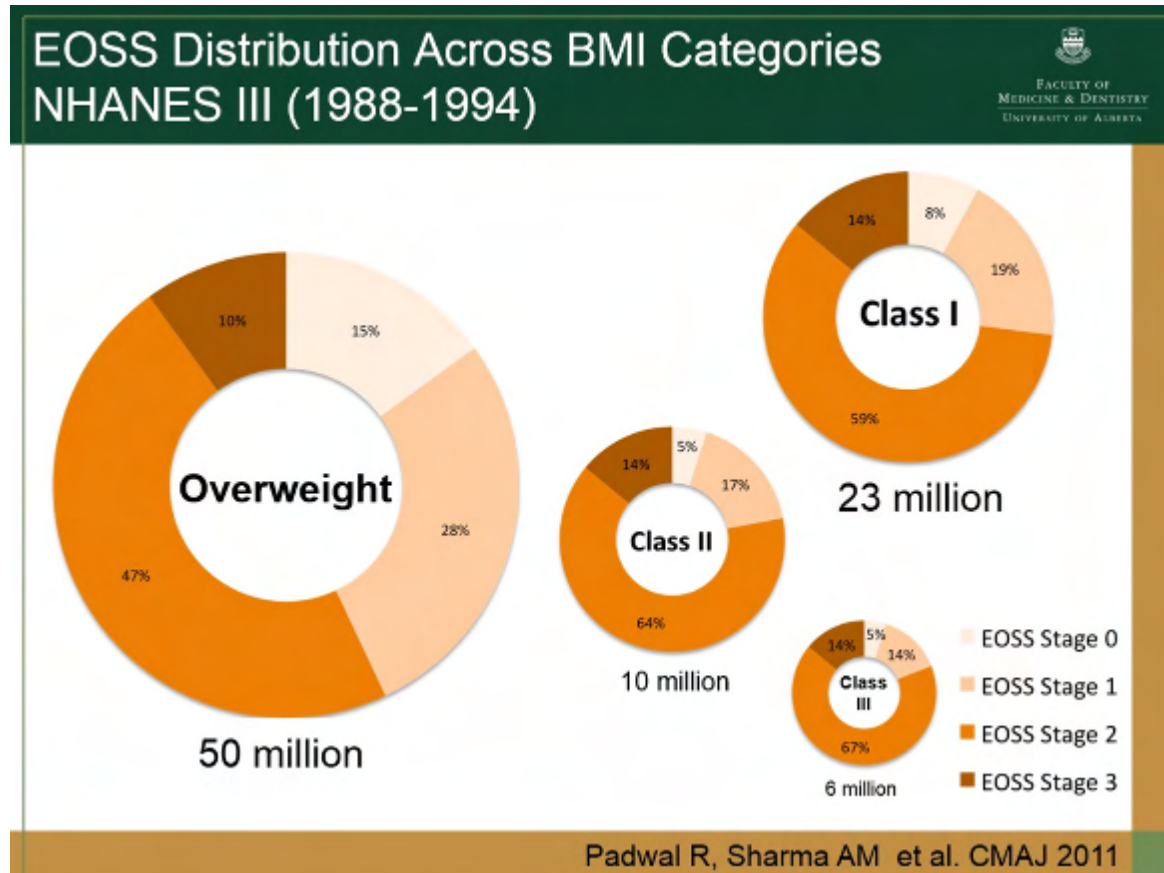
Case Example:

45 year old female with a BMI of 54 kg/m² who is in a wheel chair because of disabling arthritis, severe hyperpnea, and anxiety disorder.

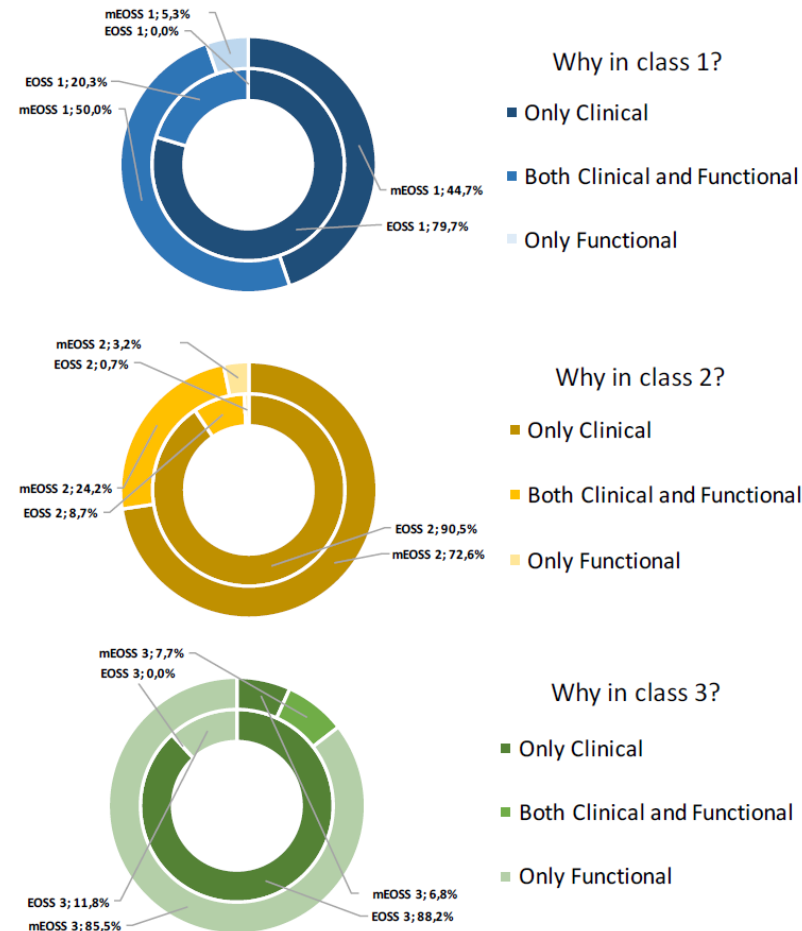
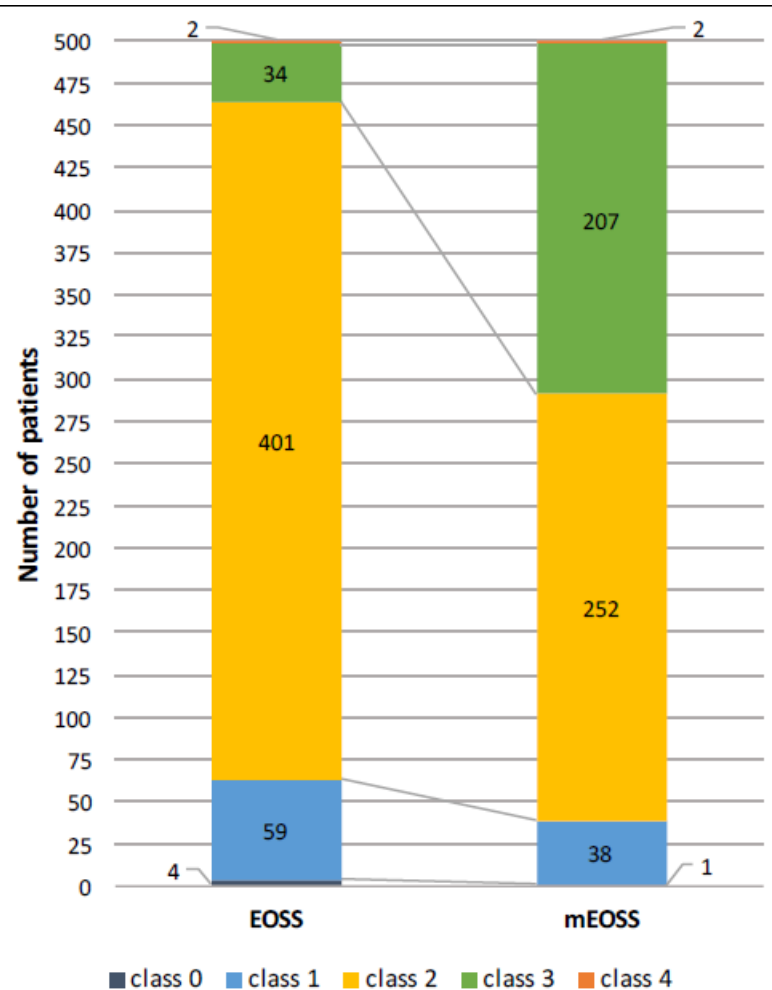
Class III, Stage 4 Obesity

Edmonton Obesity Staging System

Obesity Staging



EOSS: an improvement by Cardiopulmonary Exercise Testing



500 patients with severe obesity.

Age- and gender-appropriate VO₂peak/Kg percentiles as reported in the healthy normal-weight population of the FRIEND registry.

Obesity is chronic, relapsing, progressive disease

TAKE HOME MESSAGES

- **Obesity is a chronic disease linked to a dysfunction of the complex neuro-endocrine network that regulates our energy balance and body weight.**
- **Weight regain is facilitated by the activation of counter-regulatory mechanisms opposing weight loss.**
- **Complications of obesity are linked not only to the amount of adipose tissue, but mainly to its distribution and function (adipose-tissue based chronic disease).**
- **The complexity of obesity requires diagnostic and staging processes that should integrated anthropometric and clinical data (medical, functional and mental domains).**

Obesity is chronic, relapsing, progressive disease



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Grazie !!!



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